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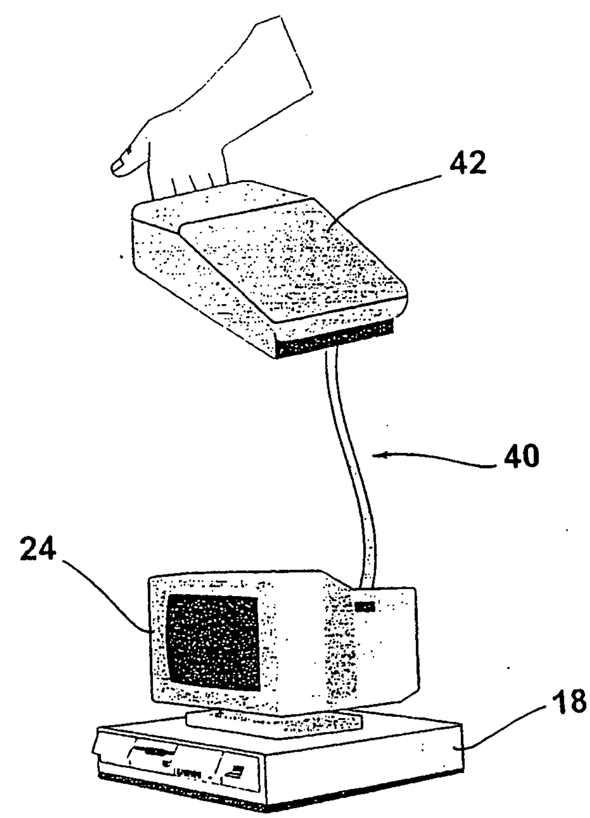
(54) Title: DEVICE FOR NONINVASIVE DETERMINATION OF BLOOD PARAMETERS

(57) Abstract

A device (10, 40) and method for noninvasively quantifying important physiological parameters in blood. The device and method utilize changes in molecular behavior induced by thermal energy of change to facilitate the measurement of the physiological parameters in blood. Oxygen saturation, partial pressure of oxygen, partial pressure of carbon dioxide, concentration of bicarbonate ion and total carbon dioxide, acid-base balance, base excess, hemoglobin level, hematocrit, oxyhemoglobin level, deoxyhemoglobin level, and oxygen content can all be determined quickly, easily, and continuously. There is no need for skin puncture or laboratory analysis.



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DEVICE FOR NONINVASIVE DETERMINATION OF BLOOD PARAMETERS

TECHNICAL FIELD

1. Field of the Invention

This invention generally relates to a noninvasive method of quantitatively determining the concentration of components in a light- or other radiation-scattering environment. A novel means of varying temperature or other parameters to assist in determinations is presented.

More particularly, the invention relates to spectrophotometry systems and measurements of behavior, action or function of substances which are affected by temperature or other variables.

A method and device for the continuous monitoring of blood parameters is especially disclosed. This technology makes use of measurement of temperature-induced changes in the respiratory molecule hemoglobin to determine acid-base balance and other parameters.

2. Description of the Related Art

There is no device currently known which can noninvasively measure pH and/or blood gases.

In a broad context, differential thermal analysis is a technique used in analytical chemistry for identifying and quantitatively analyzing the chemical composition of substances by observing the thermal behavior of a sample as it is heated. This methodology is widely used for identifying minerals and mineral structures, but is not performed noninvasively and is in fact usually destructive to the sample being tested. It is not useful in biologic applications. Similarly, related thermometric methods such as thermogravimetry, calorimetry, and cryoscopy are not related to the present invention.

Induction of temperature changes has been used in the experimental study of chemical kinetics to facilitate measurement of reaction rates. The technique described herein does not depend upon any chemical reaction taking place.

Temperature is a very important factor in the chemistry of both biologic and non-biologic systems. It reckons in the speed of reactions; indeed, if a reaction will occur at all. Temperature can be relatively easy t both measure and regulate.

Furthermore, changing the temperature of a substance or system does not normally damage the substance in any way (within a certain range; clearly temperature extremes will harm almost any system). Temperature by itself can affect acid-base balance and pH because of a direct affect on the hydrogen ion.

Spectrophotometry is a commonly used technique for the identification and quantification of substances. It is used in medicine in the form of pulse oximetry, to determine the ratio of oxyhemoglobin to deoxyhemoglobin and thus measure the oxygenation status of a patient. Spectrophotometry deals with measurement of the radiant energy transmitted or reflected by a body as a function of the wavelength. Infrared (IR) spectroscopy passes infrared light through an organic molecule and produces a spectrum that can be plotted as the amount of light transmitted versus the wavelength of infrared radiation. Since all bonds in an organic molecule interact with infrared radiation, IR spectra provide a great deal of structural data, allowing identification to be made. There is a large area of prior art relating to spectrophotometry and, more specifically, to oximetry. The most relevant prior art known by the inventor is reviewed below, but none relate to the unique determinations made possible by the method and device disclosed in this application.

U.S. patent 5,431,159, issued July 11, 1995 to Baker et al, describes methods of improving measurements made by standard pulse oximetry. While these devices may improve the signal quality and signal-to-noise ratio for oximeter calculations, they do not allow for any new determinations, as outlined in the present application.

U.S. patent 5,101,825, issued April 7, 1982 to Gravenstein et al, purports to measure hemoglobin noninvasively by means of simultaneous measurement of volume changes and changes in the mass of hemoglobin species measured by oximetry. It is unclear how blood volume changes could be determined to the desired accuracy.

U.S. patent 5,499,627, issued March 19, 1996 to Steuer et al, claims a system for noninvasive hematocrit monitoring. The patent describes techniques of measuring the infrared absorption of hemoglobin at isobestic points of the oxy and deoxy species. However, there is no discussion relating to the use of

temperature changes and, therefore, Steuer et al. is not particularly relavent to the present invention.

U.S. patent 5,427,093, issued June 27, 1995 to Ogawa et al, describes a device to disperse heat generated by the LED in an oximeter probe by means of a heat-dissipating plate. This is a potential benefit for standard pulse oximeters, but in no way improves their measurements or allow for new determinations, as in the device and method described herein.

U.S. patent 4,167,331, issued September 11, 1979 to Nielsen, teaches the use of multiple wavelength techniques for identification of multiple absorbing substances.

Several patents claim the non-invasive measurement of blood glucose using modified light radiation. U.S. patent 4,704,029, issued November 3, 1987 to Van Heuvelen, discloses the measurement of blood glucose by utilizing a refractometer. U.S. patent 5,448,992, issued September 12, 1995 to Kupershmidt, bases measurements on a polarized-modulated laser. U.S. patent 5,433,197 to Stark describes non-invasive glucose measurement using irradiation of the eye. There are many other such references, but none relate specifically to the technique of this application.

U.S. patent 4,805,623, issued February 21, 1989 to Jobsis, describes a spectrophotometric method of determining the concentration of a dilute component together with a reference component of known concentration. While not similar to the technology here disclosed, the patent teaches that obtaining an appropriate reference component is often problematic. The technique outlined in the present application obviates this lack of reference components for many cases, as determination of the concentration of many substances, such as hemoglobin level, in blood or other environments can now be done, and they in turn can serve as reference components.

U.S. patent 5,492,118, issued February 20, 1996 to Gratton et al, also discloses a technique for determining material (specifically glucose) concentrations in tissues. This is done by measuring the scattering coefficient of light passed through the tissue and comparing this with a previous scattering coefficient determined with respect to the tissue.

U.S. patent 5,402,777, issued April 4, 1995 to Warring et al, describes a device to facilitate non-invasive oxygen monitoring. This is a sensor system designed to improve the performance of a pulse oximeter under certain circumstances. While this may be a useful aid in standard pulse oximetry, it in no way enables any additional determinations to be made, as in the device described in the present invention.

Additionally, many patents disclose improvements to pulse oximeter probes or sensor as advances in the art. Included in this group is U.S. patent 5,469,845 DeLonzor et al, and many others.

3. Physiology and Biochemistry Background

This section refers specifically to hemoglobin and oximetry. Changes in many other substances secondary to thermal effects also occur, and measurements and determinations based on these effects are meant to be included within the scope of this patent application.

Hemoglobin is the molecule which is essentially entirely responsible for carrying oxygen in all vertebrates and some invertebrates (See; Nunn's Applied Respiratory Physiology, Cambridge, MA; Butterworth - Heinemann, 4th Edition (1993), Chapter 10, pp 219-246); the remainder of this discussion will be limited to humans. It is contained in the red blood cell (RBC, erythrocyte), which is the most common cell in the body. A molecule or single unit of hemoglobin (Hb) contains 4 iron groups, each of which can bind 1 molecule or unit of oxygen. Because there are 4 iron groups, a molecule of Hb can contain from 0 to 4 molecules of O_2. Hb which is carrying O_2 is known as oxyhemoglobin (HbO_2), Hb not carrying oxygen in known as deoxyhemoglobin. The relative number of O_2 molecules bound to a Hb molecule is referred to as saturation, expressed in percentage. Of course, blood is composed of billions and billions of RBCs and Hb molecules, so the averaged saturation can take on any value from 0 to 100%.

How well Hb is saturated with O_2 depends mainly on the "partial pressure" of oxygen in the blood. The higher the pressure of oxygen in the blood (PO_2), the higher the saturation (SO_2). However, the relationship between PO_2 and SO_2 is not linear (change in one is not always directly proportional to change in the

other). The dependence is described by a S-shaped "sigmoid" curve, common in the biologic sciences. This particular curve is call the Hemoglobin-Oxygen Dissociation Curve (HODC; see Figure 1). Hb absorbs O_2 in the lungs (to form HbO_2). As the RBC travels to the tissues, the HbO_2 releases oxygen.

Determination of the physiological parameters is a very important part of modern medical practice. Unfortunately, measurement of any of these parameters has until recently always required a blood sample (arterial and/or venous) to be drawn, which is then analyzed by a laboratory.

During the 1970's the first pulse oximeter was introduced. This device made use of spectrophotometry to allow approximation of arterial oxygen saturation (SaO_2), termed SpO_2 (saturation measured by pulse oximetry), by noninvasive means. After improvements, pulse oximeters are now commonplace in acute health care settings.

Pulse oximeter design and function are well documented. The two principal forms of Hb (oxy and deoxy: Hb and HbO_2) absorb different wavelengths of light to varying degrees. The standard oximeter utilizes 2 wavelengths, one in the "red" portion of the light spectrum and the other in the near-infrared. The absorbance of emissions from light-emitting diodes (LEDs) of appropriate wavelength is measured. The pulsatile (AC) and non-pulsatile (DC) components are calculated and compared, and the ratio of the corrected signal is collated to a stored calibration curve to yield SpO_2.

Transcutaneous monitoring of oxygen and carbon dioxide is also used as discussed in S.J. Barker, "Monitoring Oxygen and Carbon Dioxide", <u>International Anesthesia Research Society</u>, March 1996, pp 1-7, but there are several practical difficulties with this technology. It is dependent upon cardiac output and skin perfusion, the electrode must be calibrated before application to the skin, and the sensor's membrane and electrolyte must be replaced periodically. The only significant application has been found in neonatology.

There are many references disclosing noninvasive determination of glucose. However, no device has yet found acceptance in the marketplace for this function.

There have also been numerous attempts at monitoring using miniaturized

probes passed through arterial cannulae. The first approach employed Clark electrodes, the same oxygen electrode used In the laboratory blood-gas analyzer. More recently, the principle of florescence quenching has been used to develop fiberoptic "optodes" which can continuously monitor pH and PCO_2 as well as PO_2 through an arterial cannula. Unfortunately, there have been some technical problems with optode accuracy and reliability. While this technology will no doubt improve, it remains very costly and is of course invasive in nature.

Thus, the SO_2 can now be determined noninvasively. However, still the only way to determine pH and other parameters accurately has been by drawing a blood sample and utilizing laboratory analysis. Such analysis is obviously invasive (requires breaking the skin; any time the skin barrier is ruptured inflammation and/or infection can ensue), very painful (puncture of an artery is technically more difficult and much more painful than puncture of a vein, which is how most blood tests are performed), risks blood contamination for both the subject and the person drawing the blood, and creates toxic medical waste (syringe, needle, gloves, skin dressing, test tube or other container). It is expensive to perform, not only from the supplies and the cost of the analyzer making the measurement, but the operation of the analyzer and the drawing of the blood both require trained personnel. The analyzer must be calibrated frequently with chemical reagents which are costly and must be disposed of safely. Arterial puncture is also inherently dangerous, as it can cause a clot in the artery, and prevent blood flow "downstream", thus depriving those tissues of oxygen.

Therefore, it would be an advance in the art to provide a system and method to noninvasively and quantitatively assess acid-base balance and related variables. It would be another advance in the art to noninvasively and quantitatively measure hemoglobin level ("blood count") and oxygen content and capacity. It would be yet another improvement in the art to determine all these parameters rapidly and continuously. It would be of great betterment to make these measurements without the need for laboratory analysis, equipment, and personnel. It would be an progression to have a device with such capabilities that is easily transportable that could be used in an ambulance or when conveying a patient from one location to another.

It would be a further advance to have a device for immediate diagnosis of poisoning such as that due to carbon monoxide. It would be advantageous to allow rapid noninvasive screening of blood disorders such as sickle cell anemia.

DISCLOSURE OF INVENTION

The subject invention concerns a novel method for noninvasive determination of properties of subject matter and the environment or milieu in which the subject matter exists. The method utilizes changes in molecules induced by thermal energy to facilitate measurements. In a preferred embodiment, a new and unique method and device for noninvasive determination of oxygen saturation (SO_2), partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (PCO_2), bicarbonate ion (HCO_3^-), total carbon dioxide (TCO_2), acid-base balance (pH), base excess, total hemoglobin level (Thb), hematocrit (Hct) oxyhemoglobin level, deoxyhemoglobin level, and oxygen content is described.

The HODC is "shifted" to the left or right (as shown in Figures 2 and 3 and as discussed in the literature) by three factors: temperature, acid-base balance of the blood, and the concentration of substances called organic phosphates in the blood. The organic phosphates (the principal one is called 2,3-diphosphoglycerate: 2,3-DPG or 2,3-biphosphoglycerate: 2,3-BPG) are molecules which bind to Hb to facilitate oxygen transport. While they are important, disorders are very rare, and virtually all people can be assumed to have normal levels except in exceptional circumstances. They will not be addressed further here.

This leaves temperature and acid-base balance. The effects of these factors have been well described in the references cited. However, the only use of this information has been to "correct" values of blood samples to what they would read at standard temperature and pH.

The technology described herein utilizes the known shifts in the HODC, along with other science, to perform the measurements and calculations necessary to determine all parameters mentioned above. As mentioned, the factors which cause these shifts are well documented, as are the relative degrees of shift due to each factor. By controlling and varying temperature, one can

calculate the degree of shift due to thermal effects. Any remaining degree of shift is due to alteration in acid-base balance. As the influence of acid-base balance upon the HODC is known, alterations and status of acid-base balance can be determined.

The oximeter estimates the SO_2 of blood. Thus, it is in effect delineating a point on the HODC. Clearly, this is oblivious of any shift in the curve. By measuring SO_2 at two or more points at known temperatures, or one point where the temperature is changed to two or more different known values, one can calculate the "standard" curve. Any deviation in measured values from this curve imply an alteration in acid-base status.

In addition, the pH and PCO_2 are known to be affected by the temperature of blood, and these effects are quantified in the literature. (See, O.Siggaard-Anderson, The Acid-Base Status of the Blood, 4th Edition, pp. 29-91; Baltimore, MD; Williams & Wilkins (1974), and J.F. Nunn, Nunn's Appied Respiratory Physiology, 4th Edition, pp. 247-305; Cambridge, MA, Butterworth-Heinemann (1993).

Thus, comparison of saturation values at different known temperatures allows computation of acid-base balance and the parameters which affect it.

As the hemoglobin molecule is the primary buffer for acid-base balance in the body, estimation of hemoglobin level can be made from the degree of buffering effect (see Figure 4 and H.W. Davenport, The ABC of Acid-Base Chemistry, 5th Edition revised, pp. 8-68, Chicago, IL, University of Chicago Press (1971).

The technique of repetitious determinations made while altering temperature or other variables allows a multitude of additional analyses to be made. The determinations can be made intermittently or continuously.

The invention, together with additional features and advantages thereof, may best be understood by reference to the following description taken in connection with the accompanying illustrative drawings.

BRIEF SUMMARY OF DRAWINGS

Figure 1 is a representative graph of the normal hemoglobin-oxygen dissociation curve.

Figure 2 is a similar graph showing examples of "shifts" or alterations in the hemoglobin-oxygen dissociation curve due to changes in temperature.

Figure 3 is a similar graph showing examples of "shifts" or alterations in the hemoglobin-oxygen dissociation curve due to changes in acid-base (pH) status of the blood.

Figure 4 is a representative graph of the hemoglobin buffering effect in whole blood.

Figure 5a shows an embodiment of the invention for use on a finger. As mentioned in the text, any part of the body that can be successfully transilluminated with the radiant energy used can be utilized. Thus, toes, lips, etc. could also be used.

Figure 5b shows an embodiment of the invention using two fingers.

Figure 5c shows an embodiment of the invention using three fingers.

Figure 6 shows a close-up of an embodiment of a probe for use on a finger. The temperature induction and measurement instrumentation are included, as are radiation emission and detection means. Information would be relayed between the probe and additional components (processing, entry, and display units).

Figure 7 shows an embodiment of the invention whereby fingers are placed inside a housing. This embodiment allows multiple simultaneous measurements to be made. The radiation source, emitters and detectors, and heating/cooling means would all be contained within the casing. The processing, entry, and display units could also be housed within the casing for a single self-contained assemblage.

Figure 8 shows a close-up of an embodiment of a casing containing elements of the invention.

Figure 9 shows a close-up of an embodiment of the invention for use on tubing.

Figure 10 shows a preferred embodiment for the production and transmission of light radiation. Light of a specific wavelength and intensity is generated and transmitted to the desired site.

Figure 11 shows a standard calibration curve used in pulse oximeters. The

calibration curve is used by the oximeter to calculate arterial oxygen saturation (SaO_2) from the ratio (R) of the light absorbed (A) by the tissue being monitored.

MODE FOR CARRYING OUT THE INVENTION

Many forms of electromagnetic radiation can be used to aid in identification of, or to provide other relevant information about molecules, or substances, or their environment. The invention herein utilizes induced temperature changes to assist and improve these measurements, and enables determinations not previously possible. The description which follows is in reference to the study of blood , but can be applied to other substances as well.

All matter is affected by electromagnetic radiation and heating. The longer radio waves induce chiefly thermal agitation of molecules and excitation of molecular rotations, while infrared rays excite vibrational modes of large molecules and release fluorescent emission as well as heat. These effects are documented in standard texts and reference works of physical chemistry. However, many biologic molecules, and a great number of other substances, exhibit effects or behavior when exposed to temperature variation which are not directly attributable to thermal energy. These indirect effects can be used to aid in identification of, or to provide other relevant information about, the molecule or substance or its environment. The invention herein detailed enables measurements and determinations of these effects. The description which follows is in reference to study of the hemoglobin molecule, but extension to other substances ensues clearly.

One part of the invention consists of methods of spectrophotometry and oximetry commonly employed in the practice of medicine. Another part of the invention consists of a device used to induce temperature changes in blood or other media. Included herein are algorithms for the calculation of variables not measured directly. The algorithm outlined below serves as an example, but modifications are possible to arrive at the indicated results, and are meant to be included within the spirit or this invention. In a preferred embodiment, the invention consists of a radiation delivery device 10 for facilitating the noninvasive monitoring of a characteristic of a patient's blood parameters. The device 10 as

shown in Figures 5a-c and 6 is used to induce temperature changes in the blood. The device 10 includes a radiation emitter 12 having at least one wavelength being applied through a patient's tissue (T) to the patient's blood; a radiation detector 14 which detects reception of the at least one wavelength after absorbance through the blood; a temperature induction generator 16 for inducing temperature changes in the blood; and a controller 18 for computing the various blood parameters based on the absorbance of the at least one wavelength of radiation at various temperature levels of the blood. The radiation emitter 12, detector 14, temperature induction generator 16 are all inserted in a probe 20 which can be placed about the tissue/blood to be measured.

The probe 20 may also include a temperature sensing or measuring device 22 so that the temperature of the tissue and blood can be accurately determined. The controller 18 includes a computing device or standard personal computer (PC) with a monitor 24. Included within the controller are algorithms for the calculation of variables not measured directly. The algorithm outlined below serves as an example, but modifications are possible to arrive at the indicated results, and are meant to be included within the spirit of this application. Various additional components of the device 10 will be discussed in more detail below with reference to Examples 1-18.

The normal temperature of the human body is defined to be 37^0 centigrade, the normal pH is defined to be 7.40, and the normal base excess is defined to be 0. These values are not necessary for the practice of the invention, but serve as reference points for values in the current medical literature.

Of note, the hemoglobin level and oxygenation of the blood in the arterial circulation is the same no matter where measured, as blood is thoroughly mixed in the left heart before ejection. Thus, the probes could be on fingers, toes, lips, etc., or any combination of these.

The description is also intended to include in vitro blood containers such as tubes 30 such as shown in Figure 9. The reference numerals in Figure 9 are the same as shown in Figure 6.

The electromagnetic radiation in this description will refer to light in the visible and infrared range although, as noted in the attached claims, it is

conceivable that other forms could be used.

Similarly, while the present invention describes the use of transillumination, it will be appreciated that reflectance spectrophotometry may alternatively be employed.

The absorbance spectra for a great many substances are known, for example, that of glucose. A problem with infrared detection of glucose is that many other substances in blood have similar absorbances in regions of the infrared spectrum. This makes it difficult to differentiate glucose from these other substances. However, all infrared spectra will alter in response to temperature change. By definition, the spectra of different substances will change in different ways, because their molecular configurations are different. Thus, comparison or spectra at varying temperatures will allow separate identification.

OPERATION OF DEVICE

Incident radiation passing through a body part is attenuated (absorbed) in the tissue. The theoretical basis for spectrophotometric techniques is Beer's law (the Beer-Lambert-Bouguer law) which expresses the incident intensity in terms of transmitted intensity and extinction coefficients of the tissue compartments through which the radiation has passed. The equation can be written as:

$$\ln(I_o/I)=ECL$$

where I_o is the incident intensity of the source radiation, I is the transmitted intensity of the source through the sample, E is the extinction coefficient of the component of interest, C is the concentration of the component in the tissue itself, and L is the optical path length (distance) through the absorber. Beer's law and the practice of spectrophotometry and oximetry have been exhaustively reviewed in the literature. Pulse oximetry in effect filters out signals other that pulsating (AC). In the body, it can be assumed that the pulsatile component of the signal is arterial blood, while all other tissue absorbers should be non-pulsatile (DC).

A light signal of a known intensity and wavelength is produced by means of light-emitting diodes (LEDs) as in currently used oximeters or, as in the preferred embodiment, a broad-band light source whereby wavelengths are isolated by a rotating filter or diffusion grating. In the latter case, the emitted light is distilled

through a filter which allows a known wavelength and intensity of light to penetrate. Use of tunable lasers or other equipment is also possible.

If the light source is proximate to the point of use, no further mode of transmission will be needed. If it is not, the light will be transported to the desired point by means such as a fiber optic cable, preserving the wavelength and intensity.

Several means of temperature induction are possible. Possibilities are convection, conduction from gas or liquid, or radiant energy such as microwaves. As with the light signal, If the heating/cooling source is at or immediately adjacent to the area of need, no further transmission may be needed. If this is not the case, the means will be transported to the desired point by appropriate tubing or cabling.

Various means of temperature measurement are also possible. A large variety of electronic thermistors are commonly available. Other means such as infrared determination may also be used.

A broad-band photo detector (in the case of visible or infrared light) or other means will be utilized to measure the quantity of transmitted light. The wavelength, intensity, and timing of the emitted signal is known, allowing the extinction coefficients for the compartments through which the light passed to be calculated.

To generate a single data point, the temperature induction means is used to bring the finger (or tubing or other space of interest) to a known temperature; a temperature measurement means will be used to confirm the temperature and adjust the temperature induction means if necessary. Light of known wavelength and intensity is emitted (and transmitted if necessary) on the surface of interest. Detection of the light signal at a distinct point (normally opposing surface) is made and the relative absorbance and extinction of the signal is calculated. This measurement may be repeated one or more times to ensure the accuracy of the measurement; this can be done within a very short time frame (less than a millisecond).

To generate multiple data points, the process outlined in the previous step will be repeated at the next chosen wavelength, while still at the same predetermined temperature. In the embodiment described herein, as shown in

Figure 10, the filter 42 would be rotated so that the next wavelength filter would be adjacent to the fiber optic transmission cable. The range and number of wavelengths can be selected, and changed for different applications.

Once the desired number of wavelengths has been examined, the temperature induction means would bring the volume to a predetermined second temperature, and the data collection of steps would be repeated. At the completion of measurements and determinations for this second temperature, the temperature induction means will bring the space to a third predetermined temperature, and the measurements and determinations repeated. This process would be continued until the desired range of temperatures has been scrutinized.

The device can be operated intermittently or continuously. In the intermittent mode, a single set of calculations can be used for analysis to produce the determinations claimed. However, the device can also be easily operated in continuous mode, with the process outlined above repeated as often as wished (constantly if desired). In addition, a rapid ("stat") mode can be offered with the minimum number of measurements made that will provide an accurate estimation of correct values. Such a rapid mode would be useful in emergency situations.

While this methodology should give precise values, further adjustment may be desired to compensate for any discrepancies between theoretical and in vivo measurements. Contemporary oximeters in fact use a calibration curve when determining oxygen saturation, with the curve being generated with data from normal volunteers. A standard calibration curve for a typical oximeter is shown in Figure 11. If necessary, such a calibration or compensation curve can be created for use with these procedures for performing noninvasive.

CALCULATIONS AND ANALYSIS

The "Henderson-Hasselbach" equation, which is discussed by A. Maas, et. al,"On the reliability of the Henderson - Hasselbalch equation in routine clinical acid - base chemistry", Annals of Clinical Biochemistry, Vol. 21, pp 26-39 (1984) is well known in physiologic chemistry, describes the dissolution of an acid in terms of pH, pK (dissolution or dissociation constant), and the concentrations of the acid and its salt or base. The solubility, α , of carbon dioxide (CO_2) is temperature-dependent, and the pK for CO_2 depends on both temperature and pH. For CO_2,

the Henderson-Hasselbach equation becomes:

$$pH = pK + \log \frac{[HCO_3^-]}{\alpha\, PCO_2} ;$$

or an alternate form can be used:

since $[TCO_2]$ is very close to the sum of $[HCO_3^-]$ and $\alpha\, PCO_2$,

$[TCO_2] = [HCO_3^-] + \alpha\, PCO_2$ and

$[HCO_3^-] = [TCO_2] - \alpha\, PCO_2$; then

$$pH = pK + \log \frac{[TCO_2] - \alpha\, PCO_2}{\alpha\, PCO_2}$$

The degree of shift of the HODC is determined using calculations similar to that described below by Nunn (referenced above) and Kelman (G.R. Kelman, "Nomograms for Correction of Blood PO_2, PCO_2, pH, and Base Excess for Time and Temperature", Journal of Applied Physiology, Vol. 21, No. 5. pp 1484 - 1490, (1966)), and modified by Siggaard-Andersen (referenced above) and others, can be calculated by:

temperature factor = antilog{0.024(37-temperature)}

pH factor = antilog{0.48(pH-7.40)}

base excess factor = antilog{-0.0013 x base excess}

Calculation of blood oxygen content is made by computations similar to that of Nunn:

content (ml O_2/dl) = THb(g/dl) x SO_2 x 1.38(ml O_2/g HbO_2) + 0.003 x PO_2

Conversion of PO_2 to SO_2 is done using modifications of Adair's equation or Kelman's computation:

$$SO_2 = (25 \times (0.0257 \times PO_2 + 2 \times 0.00078 \times (PO_2)^2 + 3 \times 0.00000444 \times (PO_2)^3 + 4 \times 0.00000255 \times (PO_2)^4) / (1 + 0.0257 \times PO_2 + 0.00078 \times (PO_2)^2 + 0.00000444 \times (PO_2)^3 + 0.00000255 \times (PO_2)^4))$$

calculation of base excess can be done by the following formula or other known means:

$$\text{base excess} = (1 - 0.0143 \times Hb) \times ([HCO_3^-] - 24)$$

It should be noted that all stated formulas are subject to change and/or modification, and represent approximate values. Alterations of this algorithm will be suggested to those skilled in the art, and are meant to be included within the scope and spirit of this application.

The following algorithm describes the use of the present invention. Some variables have degrees of co-dependence. In these cases, values are calculated by iterative computational techniques.

Measurement of SO_2 is made by a first probe 12 and apparatus 10 comparable to that shown in Figures 5 and 6, using methods similar to standard oximetry described in the prior art. The probe is at a set known temperature. Calculation of PO_2 is made using computations similar to those described in the references and set forth above. For convenience, this probe may be brought to 37^0, in which case the "true PO_2" can be calculated without correction for temperature ("normalization" to 37^0). If the temperature is in fact a different value, correction may made by methods similar to those described in the references and described above.

Measurement of SO_2 is made by a second probe at a different temperature. Alternately, the temperature of the single probe can be changed, and a determination of SO_2 made at the new temperature. A higher or lower value of temperature can be used, although for ease of measurement one may be preferable.

Calculation of PO_2 is made as above. The difference in PO_2 due to the temperature difference (shift in HODC) between the two measurements is factored.

After the temperature change has been factored, any remaining difference is due to a shift in the HODC due to acid-base balance. This is primarily due to pH and only a very small component is due to base excess. The base excess can be computed by other means and then back-factored into the calculated shift in the HODC.

The "pH factor" is calculated from the ratio of the two determinations of PO_2.

Correction of the pH factor is made for the known change in pH due to change in temperature. Biochemically, temperature has an effect on the hydrogen ion distinct from the shift in the HODC.

The alteration of pH from normal (7.40) is calculated. If there is no alteration, this implies a pH of 7.40.

Now that the pH is known, computation of the carbon dioxide parameters is done using the Henderson-Hasselbach equation as described above. The effect of temperature on PCO_2 is known, as in the consequence of temperature and pH on pK. Thus, PCO_2, $[HCO_3^-]$, and $[TCO_2]$ can be computed or calculated by nomograms similar to those elucidated by Siggaard-Andersen (referenced above) and others.

Now that the pH and $[HCO_3$-] are known, computation of Hb level can be made by construction of the buffer line of blood as shown in Figure 4 (see also, Davenport, referenced above). Calculation of base excess is done as in the formula above. As mentioned, base excess can also be computed from a relative shift in the HODC, and this additional computation can serve as a confirmation of Hb level.

Oxygen content is computed as per the calculation above.

As mentioned above, modifications of this algorithm will be suggested to those skilled in the art, and are meant to be included within the scope and spirit of this application. For instance, the case of base excess was cited. Additionally, the effects of 2,3-DPG have been ignored in this description, as they are not normally considered in current clinical practice. Clearly one may wish to take these into account under certain circumstances.

Similarly, the effects oxygen and carbon dioxide have on the transport of

each other in blood are described by the Bohr and Haldane effects (together with hemoglobin level). These effects can be used to calibrate and validate results.

Following are examples which illustrate procedures for practicing the invention. These should not be construed as limiting, and that various modifications will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims.

EXAMPLE 1

A single probe 20 similar to that illustrated in Figures 5a and 6 is used. Measurement of SO_2 is made by use of a light signal 12 and photo detector 14. The heating/cooling element 16 in the probe 20 is then used to raise the temperature of the finger (F) to approximately 40^0 C A second measurement of SO_2 then is made. The algorithm outlined above is used by a computing device 18 to calculate all relevant variables which can be displayed on a monitor 24 for evaluation by a user.

A device 10 such as this might be used in place of laboratory analysis for stable patients or part of routine physical diagnosis, where the parameters are expected to change very little over the course of several minutes.

EXAMPLE 2

Two probes 26 and 28 similar to that illustrated in Figure 5b are used. The heating/cooling element 16 in one of the probes is used to raise the temperature of its finger to approximately 40^0 C. Simultaneous measurements of SO_2 are made by the two probes, one probe at body temperature and the other probe at the raised temperature. The algorithm outlined above is used to calculate all relevant variables.

Alternatively, the embodiment shown in Figures 7 and 8 is used. A device 40 such as this might be used during anesthesia for brief or low-risk surgery, where the parameters might be expected to change somewhat over the course of several minutes. The device 40 is provided with a hand and finger housing 42 which receives several fingers of a human patient within the housing. A single or

multiple probes similar to that shown in Figure 6 can be provided in the housing with respective heating/cooling elements.

EXAMPLE 3

Three probes 32, 34, and 36 similar to that illustrated in Figure 5c are used. A first probe 32 is used without heating or cooling the respective finger. The heating/cooling device 16 in a second probe 34 is used to raise the temperature of one finger to approximately 40^0 C. The heating/cooling device 16 in a third probe 36 is used to lower the temperature of a respective third finger to approximately 33^0 C. Simultaneous measurements of SO_2 are made by the three probes 32, 34, and 36. The algorithm outlined above is used by a computing device to calculate all relevant variables.

Alternatively, the embodiment shown in Figures 7 and 8 having multiple finger probes could be used.

A device such as this might be used in emergency rooms, critical care units, or during anesthesia for high-risk patients, where there is concern that the determined parameters might change very rapidly, and also where significantly lower values of SO_2 and PO_2 may occur.

EXAMPLE 4

Two probes 20 similar to that illustrated in Figure 9 are used. The heating/cooling device 16 in one of the probes is used to raise the temperature of its tubing 30 and contents to approximately 40^0 C. Simultaneous measurements of SO_2 are made by the two probes. The algorithm outlined above is used to calculate all relevant variables.

A device such as this might be used during hemodialysis, where the blood is circulated in tubing outside the body, and parameters might expected to change over the course of several minutes.

EXAMPLE 5

Three probes 20 similar to that illustrated in Figure 9 are used. The heating/cooling devices 16 in the probes are used to bring the temperatures of

three separated pieces of tubing 30 and their contents to 33°, 37°, and 40°, respectively. Simultaneous measurements of SO_2 are made by the three probes. The algorithm outlined above is used to calculate all relevant variables.

A device such as this might be used during cardiopulmonary bypass, where the blood is circulated in tubing outside the body, and parameters might be expected to change rapidly.

EXAMPLE 6

A single probe 20 similar to that illustrated in Figures 5a and 6 is used. The heating/cooling device 16 in the probe is used to vary the temperature of the finger from 33° C to 40° C in increments of 1° C. Measurements of SO_2 are made at the differing temperatures. The algorithm outlined above is used to calculate all relevant variables.

In this manner, a series of data is collected for improved accuracy in performing calculations.

Comparably, an example with a single probe 20 for tubing 30 similar to that in Figure 9 is envisioned.

EXAMPLE 7

Two or more probes 20 similar to that illustrated in Figures 5a and 6 is used. The heating/cooling device 16 in the probes are used to vary the temperatures of the fingers from 33° C to 40° C in increments of 1° C. Measurements of SO_2 are made at the differing temperatures. The algorithm outlined above is used to calculate all relevant variables.

In this manner, a series of data is collected for improved accuracy in performing the calculations.

Comparably, an example with two or more probes 20 for tubing 30 similar to that in Figure 9 is envisioned.

EXAMPLE 8

A single probe similar to that illustrated in Figures 5a, 5b, 5c, and 6 are used. Absorbance of emitted radiation over several wavelengths is measured.

A device such as this might be used to measure glucose, potassium, urea, creatinine, or other blood constituents. It could also detect substances not normally present in blood (or present in very small quantities) such as fetal hemoglobin, myoglobin, etc.

Comparably, examples with two or more probes for tissue or tubing are envisioned.

It is clear from the prior art cited that the invention described herein will measure the presence of other substances in blood in a manner equal, and in many cases superior, to current techniques.

EXAMPLE 9

A single probe 20 similar to that illustrated in Figure 9 is used. Instead of blood, measurements are made from a different body fluid such as urine, using the tubing from a bladder catheter.

A device such as this might be used to measure glucose, urea, creatinine, or the excretion of some substance in the urine

Comparably, examples with two or more probes 20 for tissue (T) or tubing 30 can be utilized as discussed above.

EXAMPLE 10

A single probe 20 similar to that illustrated in Figures 5a and 6 is used. A multitude of wavelengths is scanned. Detection of ingested drugs, medications, or other substances, or their metabolites, is made. Similarly, substances which appear within the body after other types of exposure, such as inhalation, can be measured.

Comparably, examples with two or more probes 20 for tissue (T) or tubing 30 can be utilized.

A device of this nature may be used in the workplace, hospital emergency rooms, or laboratories. Diagnosis of carbon monoxide poisoning (carboxyhemoglobin level) will be made rapidly and noninvasively. Even more importantly, the consequences of this poisoning, in the form of reduction in oxygen carrying capacity and metabolic acidosis, will be quickly known, allowing

appropriate therapy to be chosen (oxyhemoglobin, carboxyhemoglobin, oxygen content, and pH can all be measured with the present invention). The results of therapy can be monitored continuously, and as long as necessary.

EXAMPLE 11

A single probe 20 similar to that illustrated in Figures 5a and 6 is used. A multitude of wavelengths is scanned. Screening of sickle cell disease or trait or other hemoglobinopathies can be done quickly and noninvasively for large populations. Results can be confirmed by traditional laboratory analysis.

Comparably, examples with two or more probes 20 for tissue (T) or tubing 30 can also be utilized.

It is within the scope of this invention for diagnosis of other diseases or conditions which can be distinguished by markers in blood or other substances carried in blood or other body fluids. Examples include blood typing, screening of potential donors for bone marrow transplantation, certain cancers, etc.

EXAMPLE 12

Emitters and detectors can be arranged in serial pairs or a like configuration in probes similar to those in Figures 5 and 6. This would enable calculations made in the time or frequency domain, such a wave or pulse velocity. Emitters and detectors can be also grouped in parallel or concentric arrangement in probes similar to those in Figures 5 and 6. This would enable multi-dimensional analysis, comparable to computerized tomography.

EXAMPLE 13

The use of the present invention in monitoring of water or other liquids is also envisioned. A mechanism could be easily constructed whereby a modification of the invention could be placed "in-line" for the water system of a building or city. In this manner the quality and purity of the water are constantly monitored and protected. The light absorption characteristics of an enormous number of substances are known, and can thus be screened for by the method of

the present invention. Toxins, contaminants, or undesired substances can be detected and recognized quickly and easily, and appropriate measures instituted.

The sampling would not in any way affect the water or liquid, and the fluid would never leave its existing containers, such that samples would not have to be collected or disposed of in environmentally safe methods..

EXAMPLE 14

The use in monitoring of air or other gases is also envisioned. A mechanism in which samples of air from a building or industrial plant are continually monitored. As mentioned in the previous example, the light absorption characteristics of a large number of substances are well documented, and these elements can be detected using this technique. Air quality can be monitored on a constant basis. Atmospheric sampling can be performed.

EXAMPLE 15

The in vitro utilization of this invention is further envisioned. Samples of blood or other body fluids can be taken, stored, and analyzed using the device at a later point. While some characteristics of blood or biologic fluids change over time, these changes are also well known, and the original characteristics can often be inferred.

In the same line of reasoning, the invention may be used to investigate changes and alterations in blood or other substances over time or after subjecting the blood or other substance to some intervention. This is because the invention is noninvasive and nondestructive.

EXAMPLE 16

The use in remote sensing applications is possible. Infrared techniques for distant temperature sensing are in use. When combined with the present invention, one may be able to measure many biochemical processes remotely as well. This will assist in the study of atmospheric and other pollution, and a myriad of additional processes.

EXAMPLE 17

The use in environmental studies, such as the investigation of global warming, is foreseen. Substances are sought as markers which indicate temperature changes over a period of time. This invention will aid in this by identifying changes due to temperature.

EXAMPLE 18

A broad range of additional applications is envisioned. Ultraviolet and X-ray radiation are used in the technical analysis of artwork to assist in the establishment authenticity and age. Modifications of this invention will help in nondestructive testing by detection of substances within such works.

EXAMPLE 19

It is known that the infrared absorbance spectrum of water changes with temperature. The absorbance spectra of elements contained within water (contaminants, pollutants, or other substances) will also change with temperature. The spectra of these substances will change in a different manner than the spectrum of water. Thus, use of temperature pertubation or other agitation may greatly aid in analysis of such substances, without having to change the primary detection means. Many types of analysis tools and techniques currently in use could be greatly improved without large investment or retooling. Future analysis techniques could be developed utilizing this methodology to assist in measurements.

Other variables or parameters not mentioned above an also be measured or estimated. For example, the hematocrit is commonly estimated as three times the hemoglobin level. As the primary determinants of blood viscosity are temperature and hematocrit, this can be estimated, which allows additional calculations of pressure, vessel elasticity, etc.

The use of multiple or broad spectrum wavelength emission and detection (possibly combined with appropriate filters) enables the identification of a multitude of blood constituents, either naturally occurring or as the product of metabolism or

pharmacokinetics. The identification of certain substances and their concentrations allows their use as references for determination of others.

Hemoglobins are found in all classes of vertebrates, in most invertebrate phyla, and even in some plants. Other respiratory-pigments such as chlorocruorins, hemerythrins, and hemocyanins are found in other organisms. The function of all is dependent upon temperature and pH. Similarly, plants contain the molecule chorophyll in several forms. This substance is closely related to the hemoglobins of animal systems, and is also extremely sensitive to temperature changes. A multitude of other molecules, such as phosphorus compounds like the adenosine phosphates (ATP and others), found in both plants and animals, are reactive to temperature variation. The technology outlined in this patent application is relevant to measurements and determinations for all these substances and, in many cases, the environments or milieu in which they exist.

The technique may be utilized on homogeneous elements or matter which is a combination of substances.

It should be understood that the examples and embodiments described herein are for illustrative purposes only, and that various modifications and embodiments will be suggested to persons skilled in the art. The claims are meant to include all such modifications and embodiments.

CLAIMS

1. A radiation delivery device (10, 40) for facilitating the noninvasive monitoring of a characteristic of a patient's blood parameters, the device comprising:

a radiation emitter (12) having at least one wavelength being applied to the patient's blood;

a radiation detector (14) which detects reception of said at least one wavelength after absorbance through said blood;

a temperature induction generator (16) for inducing temperature changes in said blood; and

a controller (18) for computing the various blood parameters based on the absorbance of said at least one wavelength of radiation at various temperature levels of said blood.

2. The radiation delivery device (10. 40) of claim 1 wherein the radiation is selected from the group of visible light, infrared light, and ultraviolet light.

3. The radiation delivery device (10, 40) of claim 1 wherein the radiation emitter (12) has at least one wavelength being applied to a patient's tissue including blood, and said radiation detector (14) detects reception of said at least one wavelength after absorbance through said tissue.

4. The radiation delivery device (10, 40) of claim 3, wherein said tissue is selected from the group comprising hands, fingers, feet, toes, ears, earlobes, nares, lips, and tongue.

5. The radiation delivery device (10, 40) of claim 3, wherein the temperature induction generator (16) raises the temperature of the patient's tissue including blood.

6. The radiation delivery device (10, 40) of claim 5, wherein the

temperature induction generator raises the temperature of the patient's tissue including blood to about 40° c.

7. The radiation delivery device (10, 40) of claim 3, wherein the temperature induction generator (16) lowers the temperature of the patient's tissue including blood.

8. The radiation delivery device (10, 40) of claim 7, wherein the temperature induction generator (16) lowers the temperature of the patient's tissue including blood to about 33°C.

9. The radiation delivery device (10, 40) of claim 3, wherein the temperature induction generator (16) raises and lowers the temperature of the patient's tissue including blood; and

said controller (18) for computing the various blood parameters based on the absorbance of said at least one wavelength of radiation computes the various blood parameters at each of the lower, normal and higher temperature of said tissue including blood.

10. The radiation delivery device (10, 40) of claim 9, wherein the temperature levels are about 33, 37, and 40°, respectively.

11. The radiation delivery device (10, 40) of claim 1, wherein the patient's blood is carried in tubing (30), and the radiation emitter (12) is being applied to said tubing and contents, the radiation detector (14) is detecting through said tubing and contents, said temperature induction generator (16) is inducing temperature changes in said tubing and contents, and said controller (18) is computing the various blood parameters based on the absorbance of said at least one wavelength of radiation at various temperature levels of said tubing and contents.

12. A radiation delivery device (10, 40) of claim 11, where in the

temperature induction generator (16) raises and lowers the temperature of the tubing and blood contents; and

the controller (18) for computing the various blood parameters measures the absorbance of said radiation at the lower, normal and higher temperature of said tubing and blood contents.

13. A radiation delivery device (10,40) of claim 1, further comprising a plurality of radiation emitters (12), matching radiation detector (14) and generators (16), each matching emitter, detector and temperature induction generator being able to be set at different temperature levels so that said controller can simultaneously measure the absorbance of said radiation at said various temperature levels of said blood.

14. A device (10, 40) to detect and measure elements of the blood, including, but not limited to, hemoglobin in any of its forms, comprising

an emission means (12);

a detecting means (14) which detects reception of said emission means after contact with the blood;

means (16) of inducting a temperature change in the blood;

means (22) of measuring the temperature of the blood;

a controller means (18) for computing the various blood elements based on the contact of said radiation from said emissions means at various temperature levels of the blood, the controller having an input means (18) to allow various changes in the emission means, detecting means, and temperature inducting means;

and a display means (24) to relay the various blood elements to an end user of the device.

15. A device (10,40) of claim 14, wherein the detector means (14) detects the radiation emitted by said emission means (12).

16. A device (10,40) of claim 15, wherein the radiation emitted by said

emission means (12) is selected from the group comprising visible light, infrared light, and ultraviolet light.

17. A device (10,40) of claim 15, wherein the means (16) of induction of temperature changes in said blood is selected from the group comprising conduction, convection and radiation.

18. A device (10,40) of claim 14, wherein the means (22) to measure temperature of said blood is selected from the group comprising electronic, and infrared.

19. A device (10,40) of claim 14, further comprising of plurality of emission means (12), detection means (14), means (16) for induction of temperature, and means (22) for measuring temperature.

20. A method for noninvasively determining one or more of the following blood parameters; total hemoglobin, oxygen saturation, partial pressure of oxygen, partial pressure of carbon dioxide, bicarbonate ion, total carbon dioxide, acid-base balance, base excess, oxyhemoglobin, deoxyhemoglobin, and oxygen content, in an animal or human, said method comprising of steps of:

emitting radiation (12) having at least one wavelength to the blood;

detecting (14) said radiation having at least one wavelength after contact with the blood;

inducing (16) a temperature change in said blood while emitting and detecting said radiation through the blood; and

computing (18) the various blood parameters based on the contact of said at least one wavelength of radiation at various temperature levels of the blood.

21. The method of claim 20, wherein said detecting step (14) is selected from the group comprising detecting said radiation after absorbance, reflection, and any combination thereof with the blood.

22. The method of claim 20, wherein said radiation is selected from the group comprising visible light, infrared light, and ultraviolet light, or any combination thereof.

23. The method of claim 20, wherein the inducing (16) a temperature change step includes conduction, convection, and radiation or any combination thereof.

24. The method of claim 20, further including a step of measuring (22) the temperature of the blood.

25. The method of claim 20, wherein said emitting step (12) includes the emission of a plurality of wavelengths to the blood.

26. The method of claim 20, wherein said blood is contained in animal or human tissue and the radiation is being emitted to contact said tissue.

27. The method of claim 26, wherein said tissue is selected from the group comprising hands, feet, toes, ears, earlobes, nares, lips, and tongue.

28. The method of claim 20, wherein said blood is contained in a tube (30) outside of the animal or human tissue and the radiation is being emitted through said tube.

29. The method of claim 20, wherein the emitting step (12) includes a plurality of emitters (12) having at least one wavelength, and the detecting step (14) includes a plurality of detectors (14) for detecting the radiation from said emitters.

30. A device (10,40) for noninvasively determining characteristics of subject matter and the environment in which the subject matter exists, the device comprising:

an emitter means (12) having at least one wavelength of electromagnetic radiation applied to the subject matter;

a detector means (14) which senses and measures reception of said wavelength after contact with the subject matter;

a temperature induction means (16) for generating temperature changes in the subject matter; and

a controller (18) for manipulating said emitter means, detector means, and temperature inductors means and for computing parameters based on information processed from the contact of said radiation at various temperature levels on the subject matter.

31. A device (10,40) of claim 30, wherein the subject matter is a living organism and the characteristics determined are the temperature induced changes in biologic molecules.

32. A device (10,40) of claim 30, wherein the detector means (14) senses and measures reception of said wavelength after absorbance through said subject matter.

33. A device (10,40) of claim 30, wherein the detector means (14) senses and measures reception of said wavelength after reflection from the subject matter.

34. A device (10,40) of claim 30, wherein the detector means (14) senses and measures reception of said wavelength after refractance from the subject matter.

35. The device (10,40) of claim 30, wherein the emitter means (12) and detector means (14) are arranged serially thereby allowing calculations in time and frequency parameters, such as velocity of wave and pulse flow.

36. The device (10,40) of claim 30, wherein the emitter means (12) and

detector means (14) are arranged in a parallel manner, thereby allowing calculations in more than one physical dimension, such as amplitude.

37. A device (10,40) according to claim 30, utilizing induced changes in temperature to effect alterations in the hemoglobin-oxygen dissociation curve, for noninvasively determining one or more of the following blood parameters;

oxygen saturation, partial pressure of oxygen, partial pressure of carbon dioxide, concentration of bicarbonate ion and total carbon dioxide, acid-base balance, base excess, hemoglobin level, oxyhemoglobin level, deoxyhemoglobin level, and oxygen content.

38. A method for facilitating the noninvasive determination of characteristics of subject matter and the environment in which said subject matter exists, the method comprising the steps of:

emitting (12) at least one wavelength of electromagnetic radiation applied to said subject matter

detecting (14) said wavelength(s) after contact with said subject matter;

inducing (16) a temperature change in said subject matter while emitting and detecting said radiation being applied to said subject matter; and

computing (18) parameters based on information processed from the contact of said radiation at various temperature levels on said subject matter.

39. The method of claim 38, wherein said detection step (14), is selected from the group comprising detecting said radiation after absorbance, reflection, and any combination thereof with the subject matter.

40. The method of claim 38, wherein the inducing (16) a temperature change step includes conduction, convection, and radiation or any combination thereof.

41. The method of claim 38, further including the step (22) of measuring the temperature of the subject matter.

42. The method of claim 38, wherein said emitting step (12) includes the emission of a plurality of wavelengths to the subject matter.

43. A method for determination of hemoglobin level by means of measuring hemoglobin buffering effect in blood, the method comprising the steps of:

determining the pH of the blood in accordance with the method of the present invention,

calculating the bicarbonate ion in accordance with the method of the present invention, and

estimating the hemoglobin buffering effect by comparing the pH and bicarbonate ion levels together, then computing the total hemoglobin level therefrom.

Hemoglobin-Oxygen Dissociation Curve

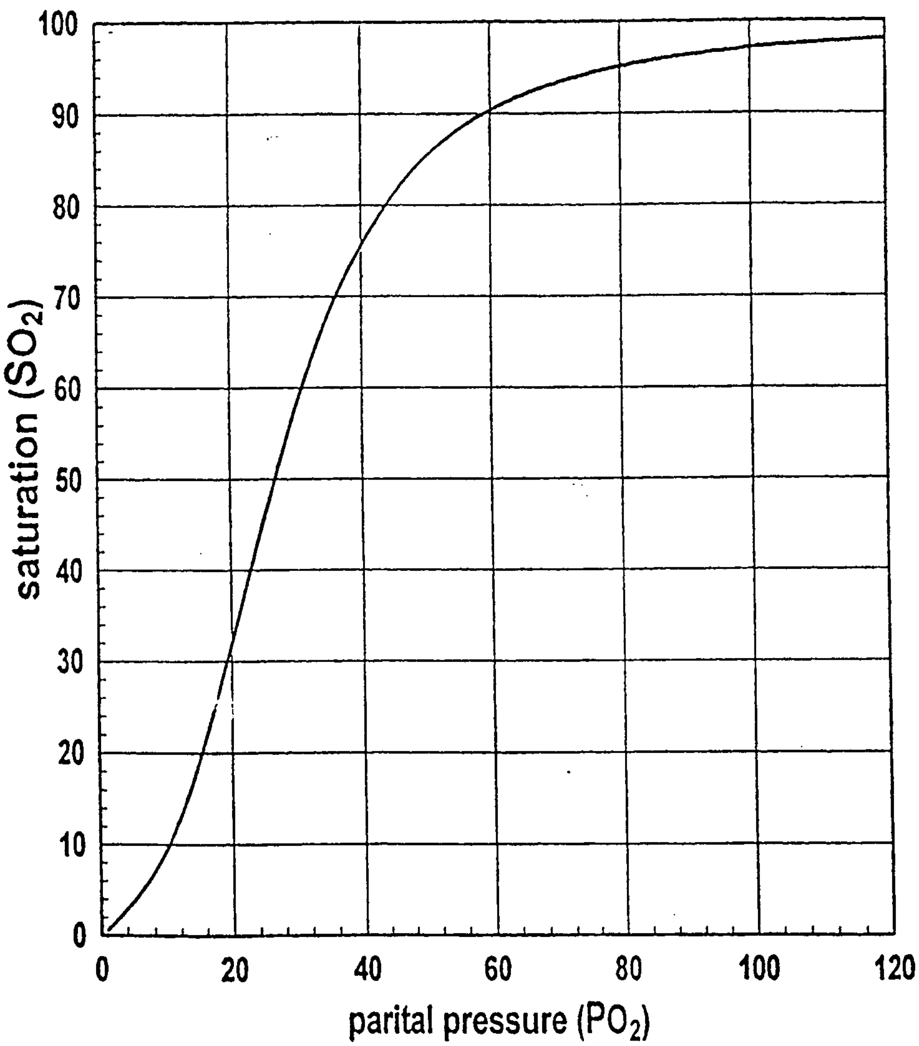


Figure 1

shifts in the HODC due to temperature

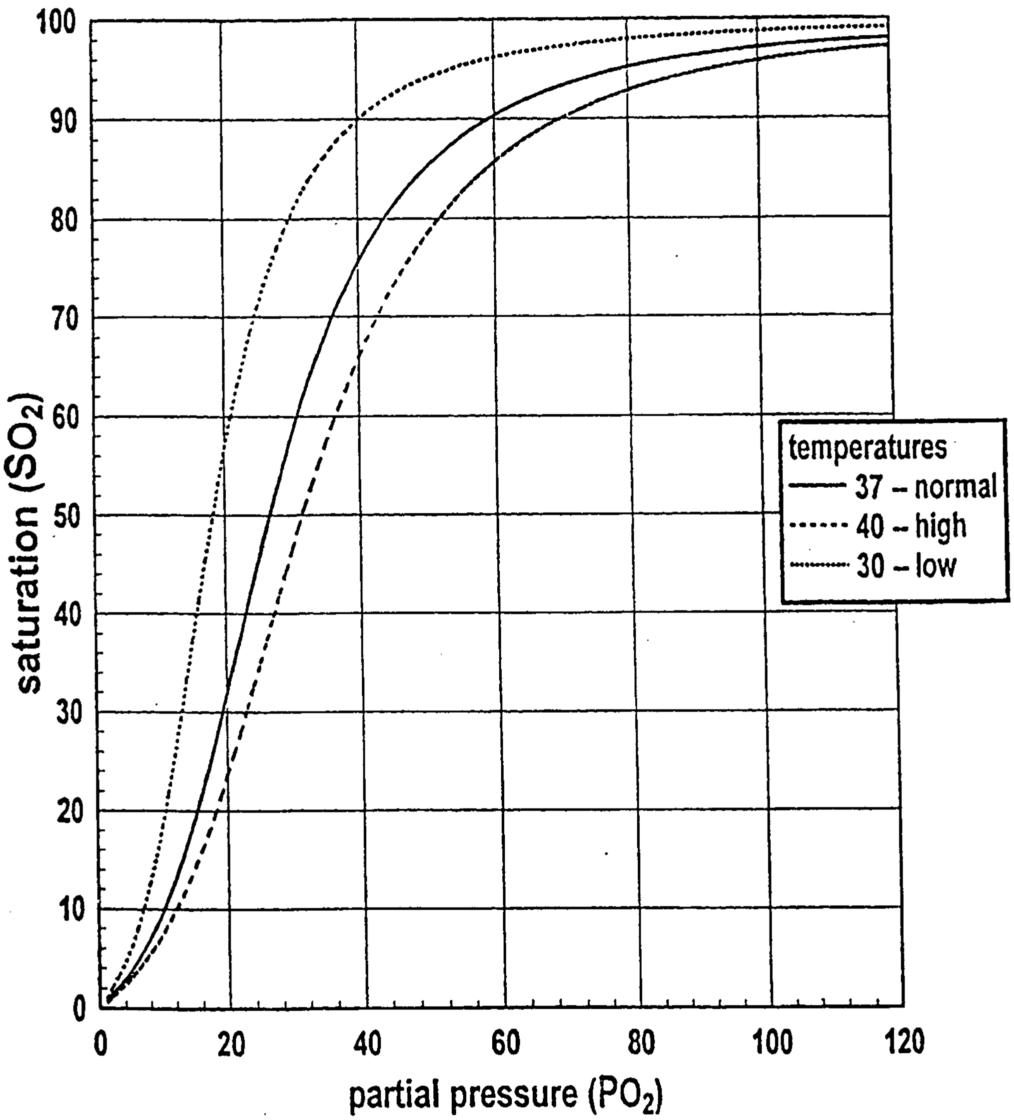
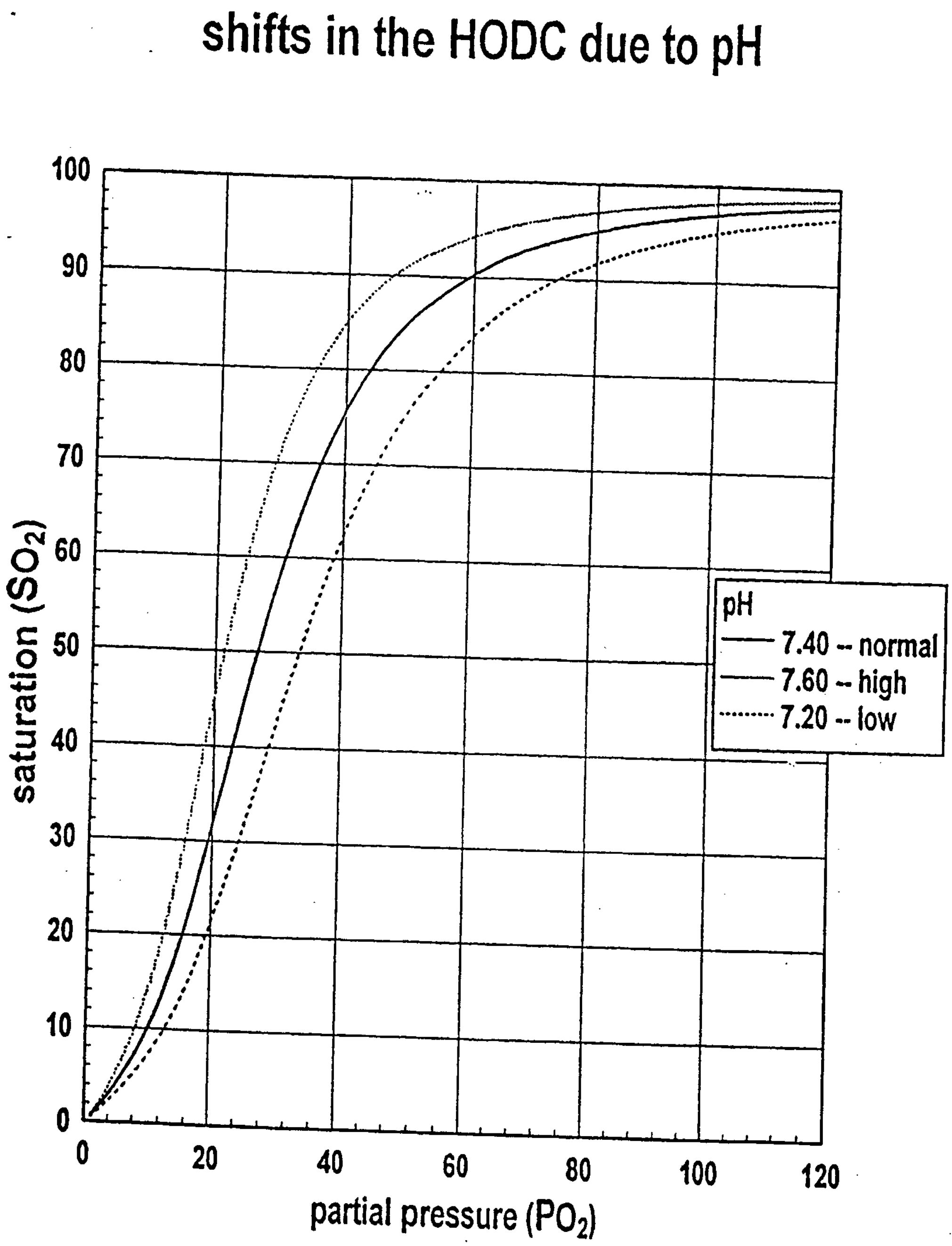


Figure 2



shifts in the HODC due to pH
100
90
80
70
60
50
40
30
20
10
0
saturation (SO_2)
0
20
40
60
80
100
120
partial pressure (PO_2)
pH
7.40 -- normal
7.60 -- high
7.20 -- low

Figure 3

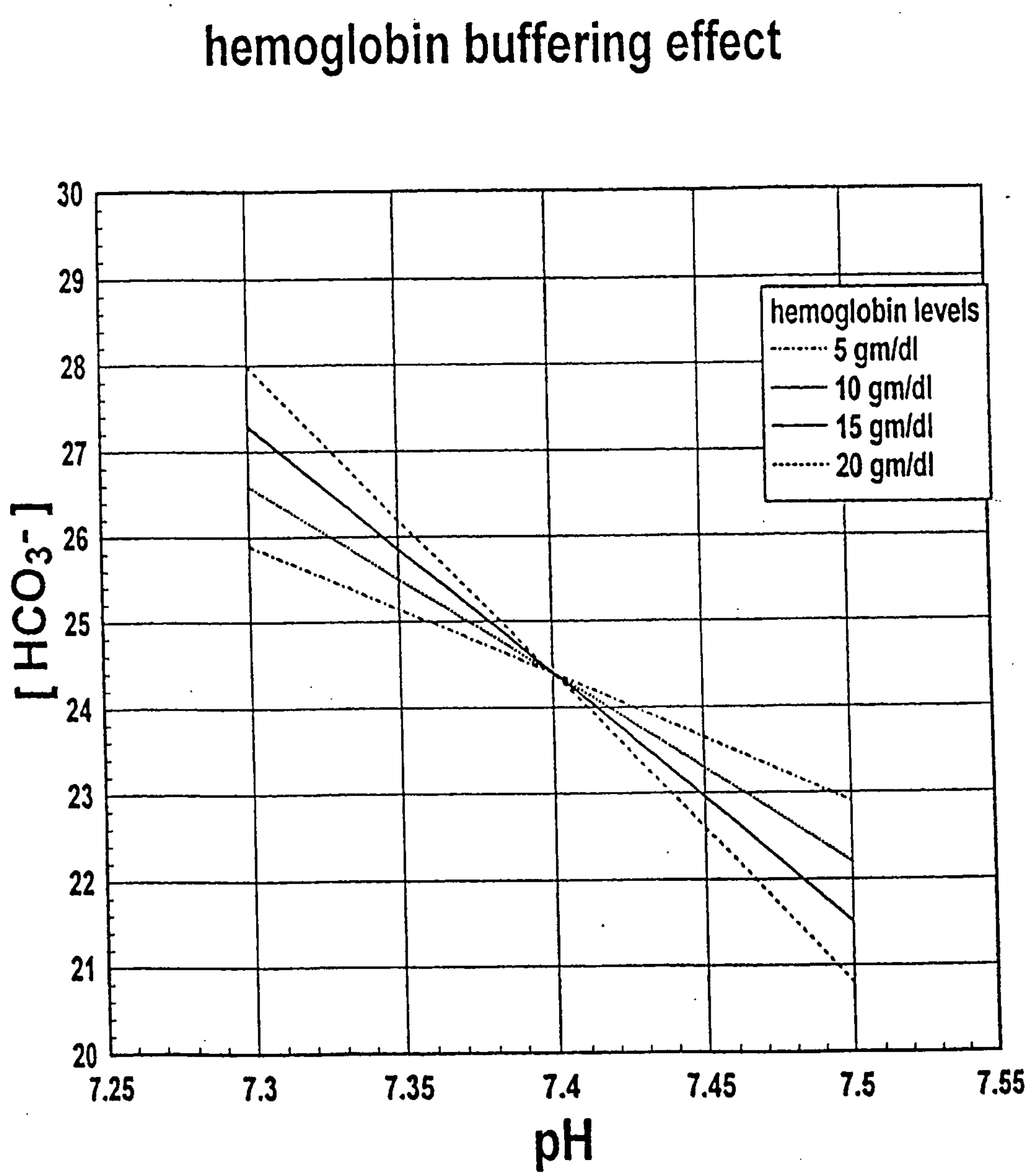

hemoglobin buffering effect
30
29
28
27
26
25
24
23
22
21
20
[HCO_3^-]
7.25
7.3
7.35
7.4
7.45
7.5
7.55
pH
hemoglobin levels
5 gm/dl
10 gm/dl
15 gm/dl
20 gm/dl

Figure 4

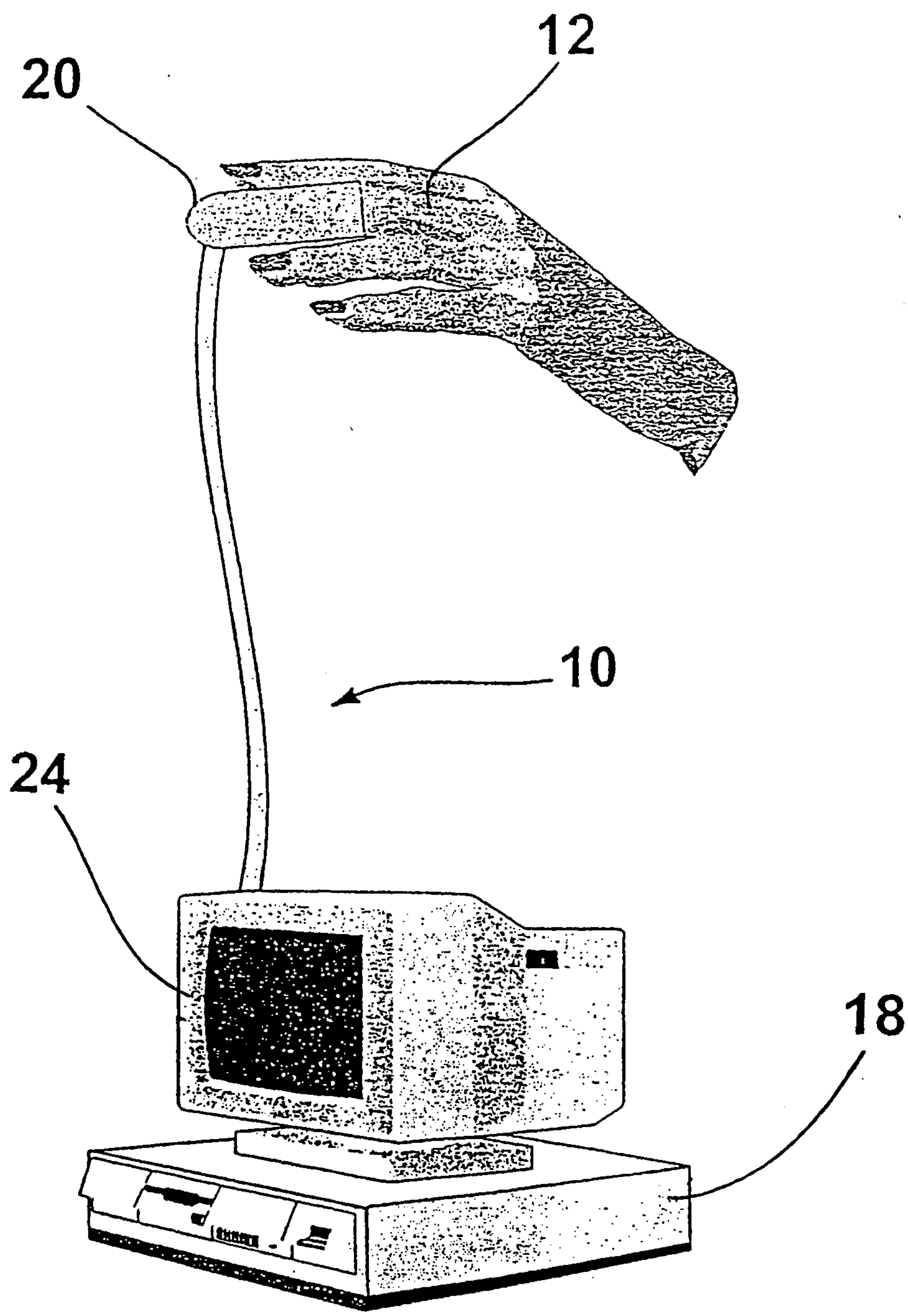


Figure 5a

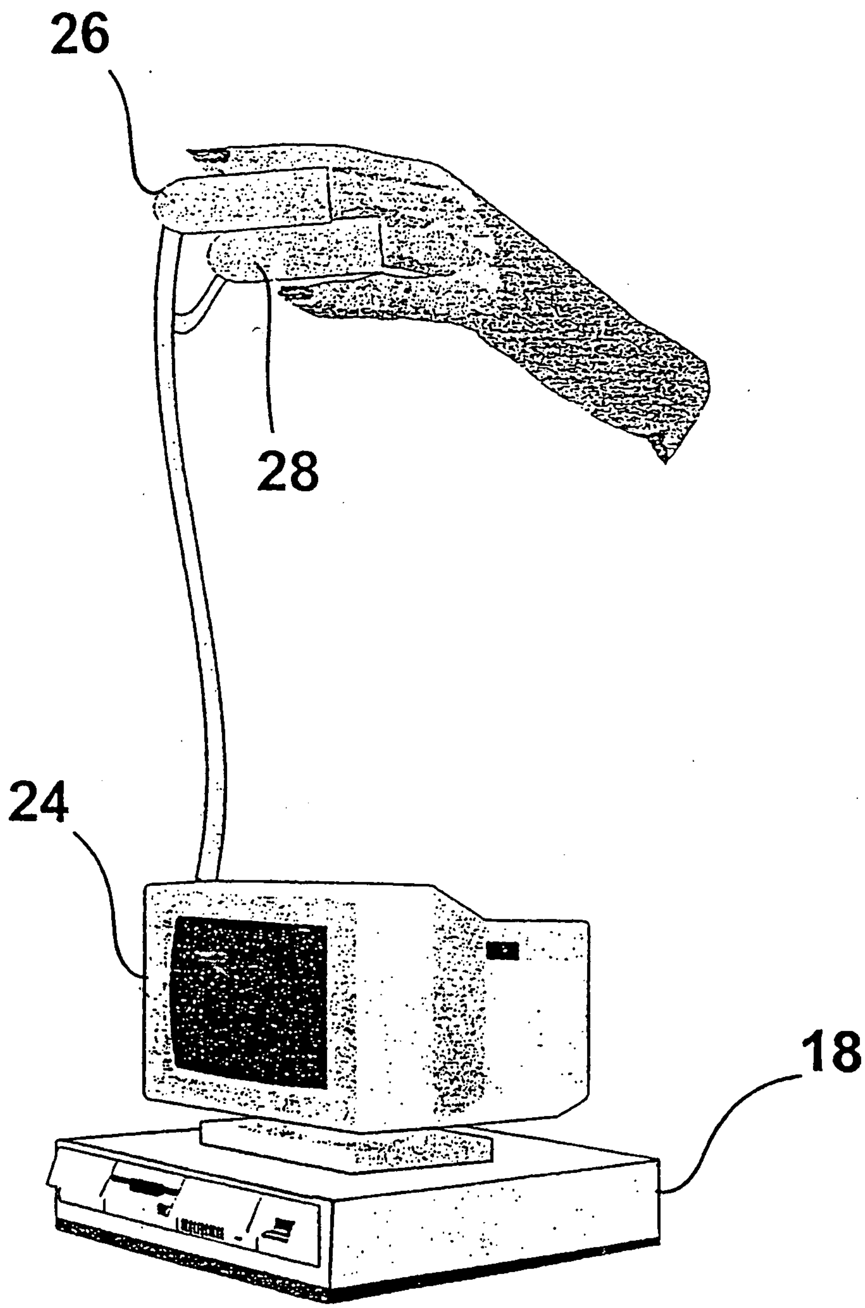


Figure 5b

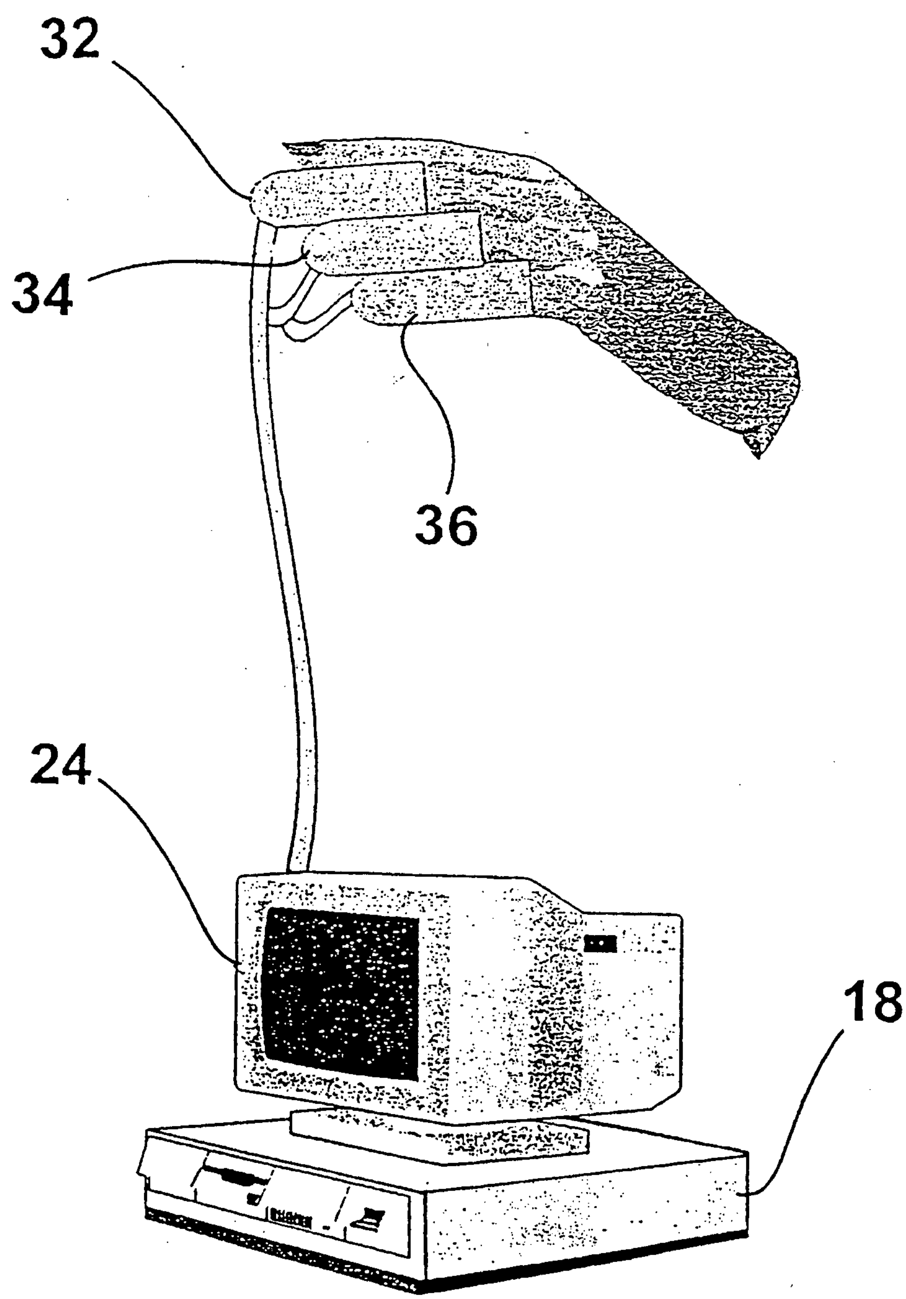


Figure 5c

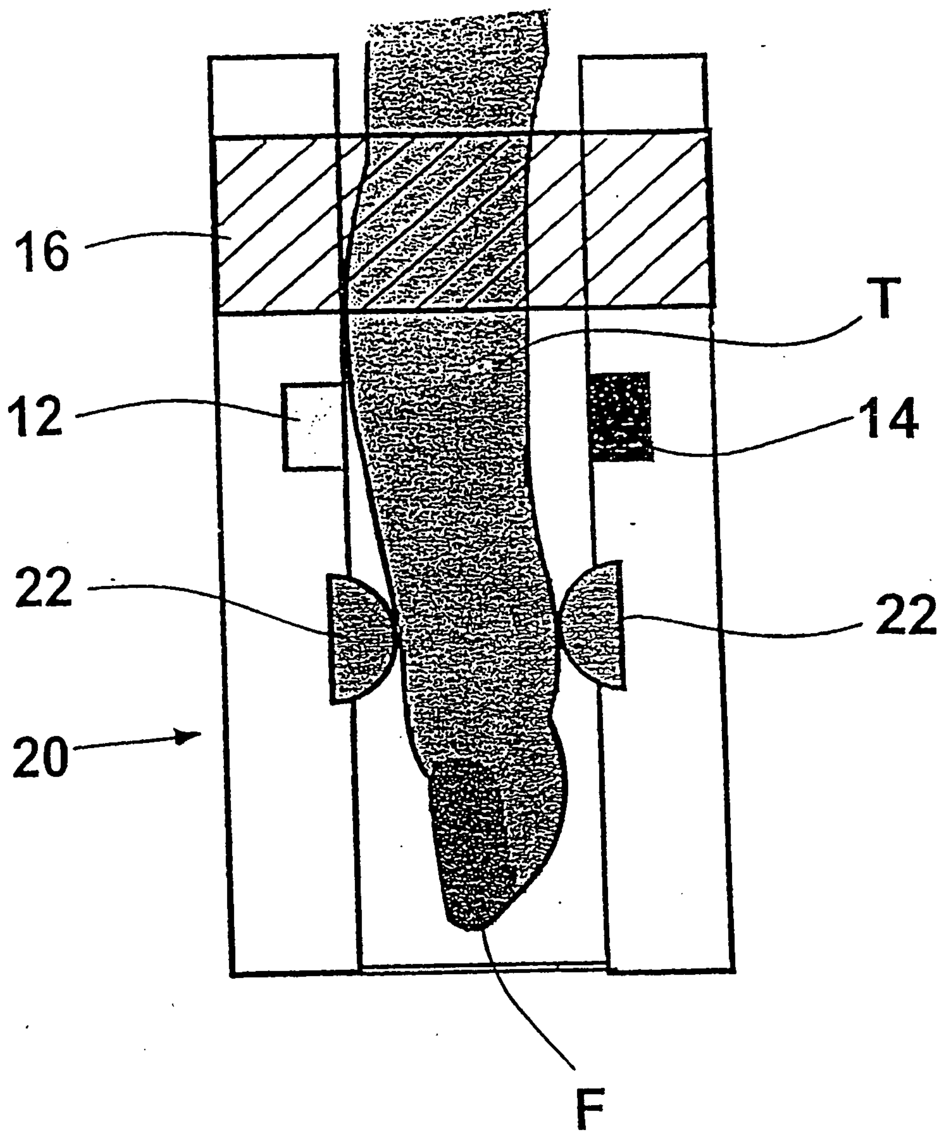


Figure 6

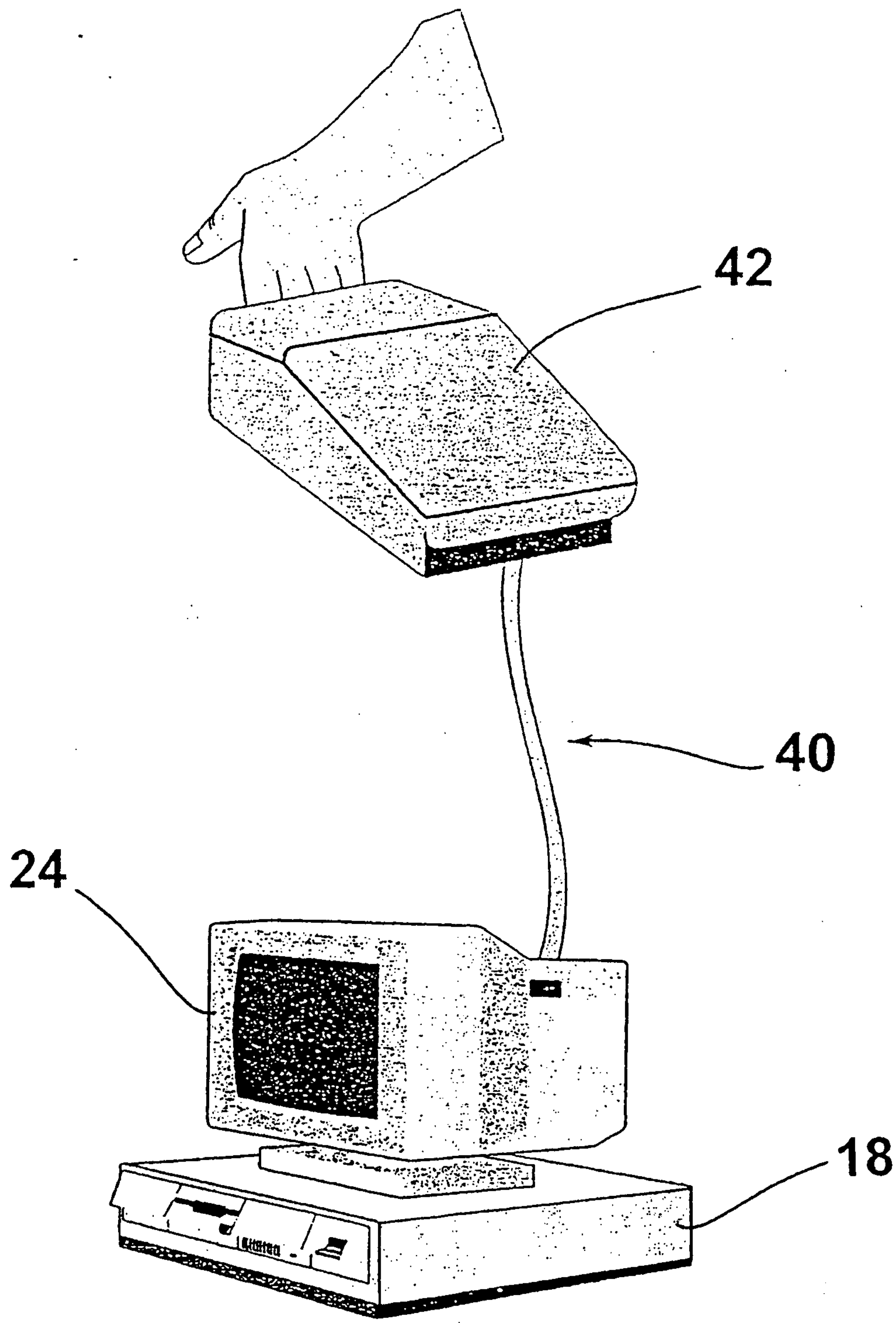


Figure 7

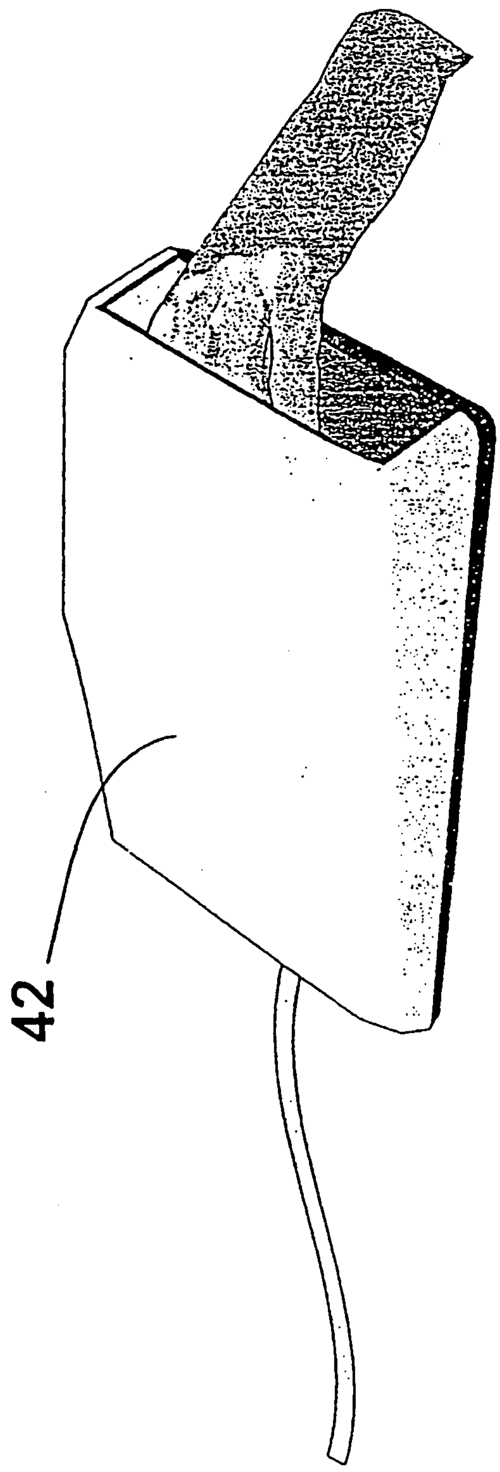


Figure 8

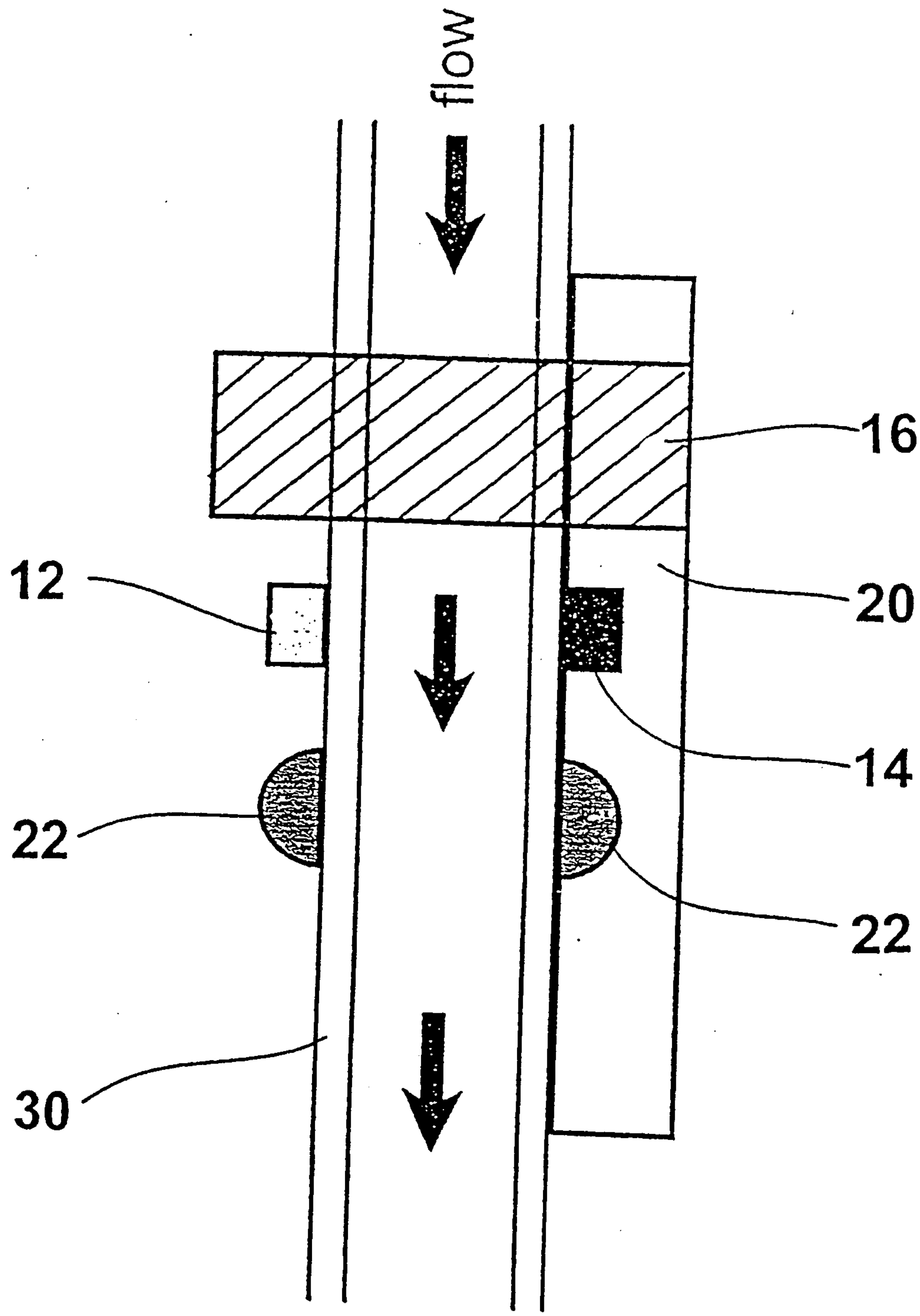


Figure 9

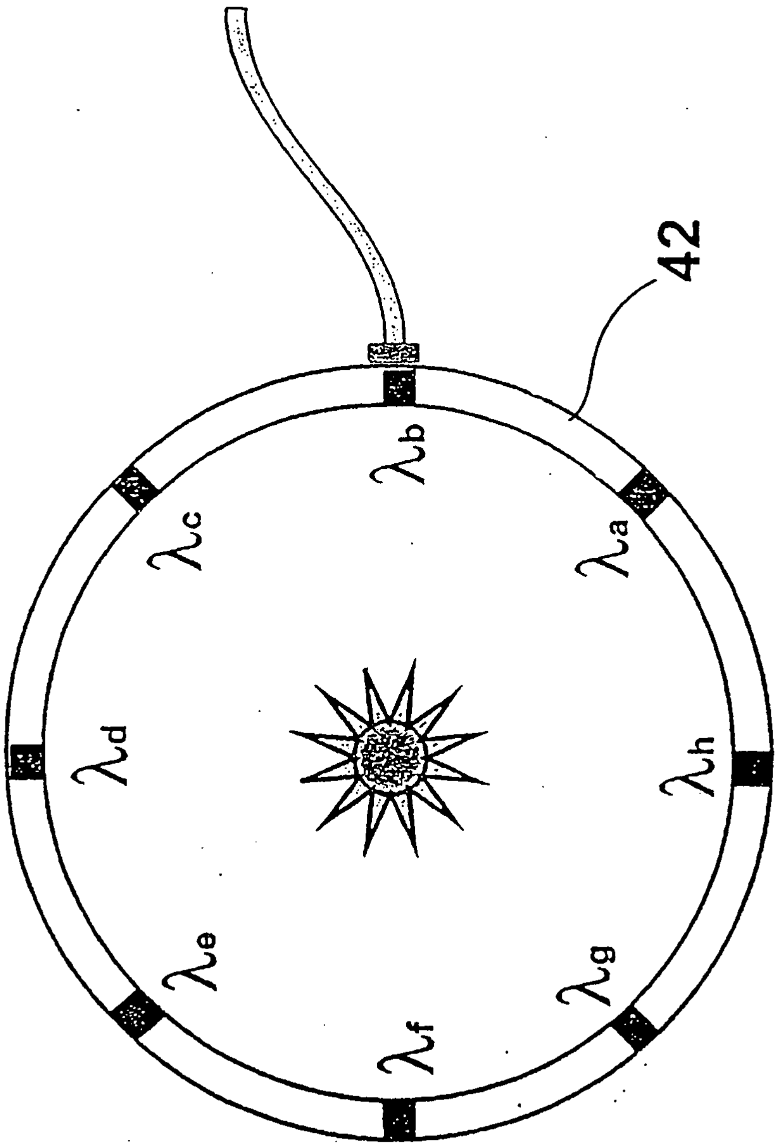

42
λ_a
λ_b
λ_c
λ_d
λ_e
λ_f
λ_g
λ_h

Figure 10

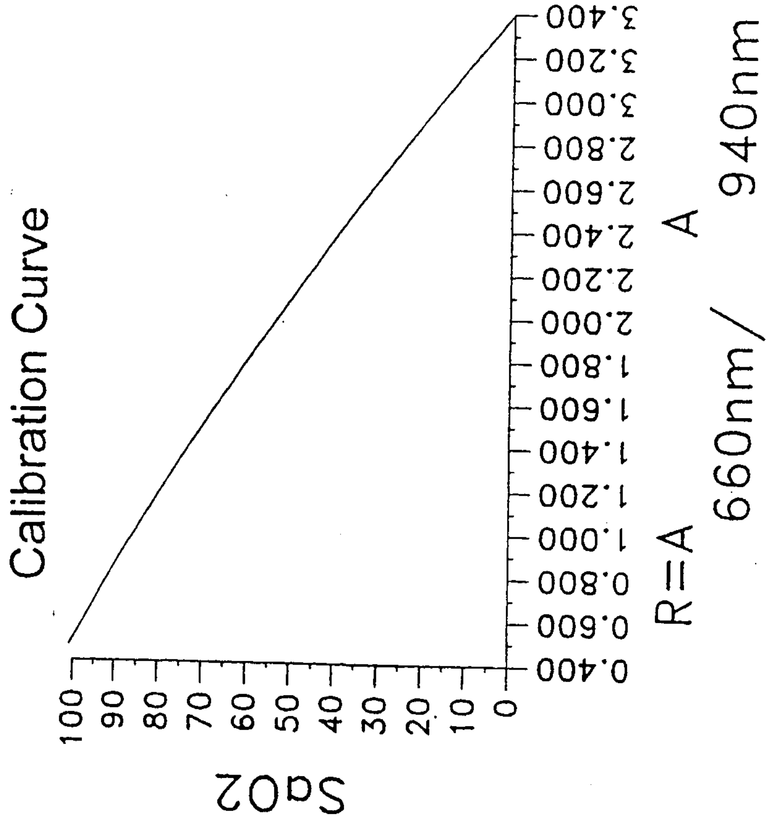

Calibration Curve
SaO2
100
90
80
70
60
50
40
30
20
10
0
0.400
0.600
0.800
1.000
1.200
1.400
1.600
1.800
2.000
2.200
2.400
2.600
2.800
3.000
3.200
3.400
R=A 660nm / A 940nm

Figure 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/11895

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61B 5/00
US CL :356/39; 600/334
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 356/39, 41; 600/322, 323, 326, 334

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 4,926,867 A (KANDA ET AL) 22 MAY 1990, ENTIRE DOCUMENT.	1-6 --- 11, 12
X --- Y	US 5,131,391 A (SAKAI ET AL) 21 JULY 1992, ENTIRE DOCUMENT.	14-18, 20-27, 30, 32, 33, 38-42 --- 19, 28, 29, 31, 34-37
X --- Y	US 5,190,039 A (TAKEUCHI ET AL) 02 MARCH 1993, ENTIRE DOCUMENT.	43 --- 31, 37

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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Date of the actual completion of the international search	Date of mailing of the international search report
23 FEBRUARY 1998	17 MAR 1998

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	ERIC F. WINAKUR
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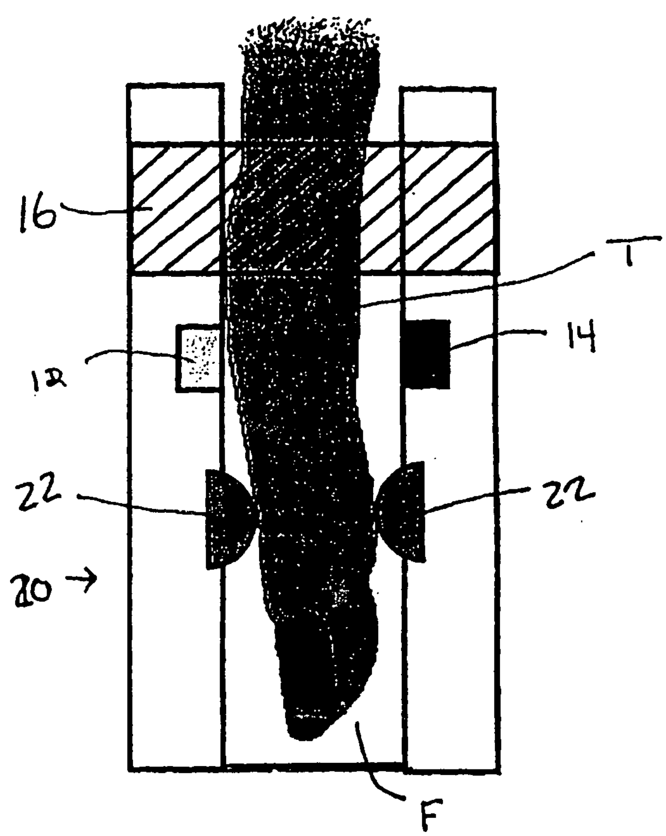
(54) Title: DEVICE FOR NONINVASIVE DETERMINATION OF BLOOD PARAMETERS

(57) Abstract

A device (10, 40) and method for noninvasively quantifying important physiological parameters in blood. The device and method utilize changes in molecular behavior induced by thermal energy of change to facilitate the measurement of the physiological parameters in blood. Oxygen saturation, partial pressure of oxygen, partial pressure of carbon dioxide, concentration of bicarbonate ion and total carbon dioxide, acid-base balance, base excess, hemoglobin level, hematocrit, oxyhemoglobin level, deoxyhemoglobin level, and oxygen content can all be determined quickly, easily, and continuously. There is no need for skin puncture or laboratory analysis.



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DEVICE FOR NONINVASIVE DETERMINATION OF BLOOD PARAMETERS

TECHNICAL FIELD

1. Field of the Invention

This invention generally relates to a noninvasive method of quantitatively determining the concentration of components in a light- or other radiation-scattering environment. A novel means of varying temperature or other parameters to assist in determinations is presented.

More particularly, the invention relates to spectrophotometry systems and measurements of behavior, action or function of substances which are affected by temperature or other variables.

A method and device for the continuous monitoring of blood parameters is especially disclosed. This technology makes use of measurement of temperature-induced changes in the respiratory molecule hemoglobin to determine acid-base balance and other parameters.

2. Description of the Related Art

There is no device currently known which can noninvasively measure pH and/or blood gases.

In a broad context, differential thermal analysis is a technique used in analytical chemistry for identifying and quantitatively analyzing the chemical composition of substances by observing the thermal behavior of a sample as it is heated. This methodology is widely used for identifying minerals and mineral structures, but is not performed noninvasively and is in fact usually destructive to the sample being tested. It is not useful in biologic applications. Similarly, related thermometric methods such as thermogravimetry, calorimetry, and cryoscopy are not related to the present invention.

Induction of temperature changes has been used in the experimental study of chemical kinetics to facilitate measurement of reaction rates. The technique described herein does not depend upon any chemical reaction taking place.

Temperature is a very important factor in the chemistry of both biologic and non-biologic systems. It reckons in the speed of reactions; indeed, if a reaction will occur at all. Temperature can be relatively easy t both measure and regulate. Furthermore, changing the temperature of a substance or system does not

normally damage the substance in any way (within a certain range; clearly temperature extremes will harm almost any system). Temperature by itself can affect acid-base balance and pH because of a direct affect on the hydrogen ion.

Spectrophotometry is a commonly used technique for the identification and quantification of substances. It is used in medicine in the form of pulse oximetry, to determine the ratio of oxyhemoglobin to deoxyhemoglobin and thus measure the oxygenation status of a patient. Spectrophotometry deals with measurement of the radiant energy transmitted or reflected by a body as a function of the wavelength. Infrared (IR) spectroscopy passes infrared light through an organic molecule and produces a spectrum that can be plotted as the amount of light transmitted versus the wavelength of infrared radiation. Since all bonds in an organic molecule interact with infrared radiation, IR spectra provide a great deal of structural data, allowing identification to be made. There is a large area of prior art relating to spectrophotometry and, more specifically, to oximetry. The most relevant prior art known by the inventor is reviewed below, but none relate to the unique determinations made possible by the method and device disclosed in this application.

U.S. patent 5,431,159, issued July 11, 1995 to Baker et al, describes methods of improving measurements made by standard pulse oximetry. While these devices may improve the signal quality and signal-to-noise ratio for oximeter calculations, they do not allow for any new determinations, as outlined in the present application.

U.S. patent 5,101,825, issued April 7, 1982 to Gravenstein et al, purports to measure hemoglobin noninvasively by means of simultaneous measurement of volume changes and changes in the mass of hemoglobin species measured by oximetry. It is unclear how blood volume changes could be determined to the desired accuracy.

U.S. patent 5,499,627, issued March 19, 1996 to Steuer et al, claims a system for noninvasive hematocrit monitoring. The patent describes techniques of measuring the infrared absorption of hemoglobin at isobestic points of the oxy and deoxy species. However, there is no discussion relating to the use of temperature changes and, therefore, Steuer et al. is not particularly relavent to the present invention.

U.S. patent 5,427,093, issued June 27, 1995 to Ogawa et al, describes a

device to disperse heat generated by the LED in an oximeter probe by means of a heat-dissipating plate. This is a potential benefit for standard pulse oximeters, but in no way improves their measurements or allow for new determinations, as in the device and method described herein.

U.S. patent 4,167,331, issued September 11, 1979 to Nielsen, teaches the use of multiple wavelength techniques for identification of multiple absorbing substances.

Several patents claim the non-invasive measurement of blood glucose using modified light radiation. U.S. patent 4,704,029, issued November 3, 1987 to Van Heuvelen, discloses the measurement of blood glucose by utilizing a refractometer. U.S. patent 5,448,992, issued September 12, 1995 to Kupershmidt, bases measurements on a polarized-modulated laser. U.S. patent 5,433,197 to Stark describes non-invasive glucose measurement using irradiation of the eye. There are many other such references, but none relate specifically to the technique of this application.

U.S. patent 4,805,623, issued February 21, 1989 to Jobsis, describes a spectrophotometric method of determining the concentration of a dilute component together with a reference component of known concentration. While not similar to the technology here disclosed, the patent teaches that obtaining an appropriate reference component is often problematic. The technique outlined in the present application obviates this lack of reference components for many cases, as determination of the concentration of many substances, such as hemoglobin level, in blood or other environments can now be done, and they in turn can serve as reference components.

U.S. patent 5,492,118, issued February 20, 1996 to Gratton et al, also discloses a technique for determining material (specifically glucose) concentrations in tissues. This is done by measuring the scattering coefficient of light passed through the tissue and comparing this with a previous scattering coefficient determined with respect to the tissue.

U.S. patent 5,402,777, issued April 4, 1995 to Warring et al, describes a device to facilitate non-invasive oxygen monitoring. This is a sensor system designed to improve the performance of a pulse oximeter under certain circumstances. While this may be a useful aid in standard pulse oximetry, it in no wav enables anv additional determinations to be made. as in the device described

in the present invention.

Additionally, many patents disclose improvements to pulse oximeter probes or sensor as advances in the art. Included in this group is U.S. patent 5,469,845 DeLonzor et al, and many others.

3. Physiology and Biochemistry Background

This section refers specifically to hemoglobin and oximetry. Changes in many other substances secondary to thermal effects also occur, and measurements and determinations based on these effects are meant to be included within the scope of this patent application.

Hemoglobin is the molecule which is essentially entirely responsible for carrying oxygen in all vertebrates and some invertebrates (See; Nunn's Applied Respiratory Physiology, Cambridge, MA; Butterworth - Heinemann, 4th Edition (1993), Chapter 10, pp 219-246); the remainder of this discussion will be limited to humans. It is contained in the red blood cell (RBC, erythrocyte), which is the most common cell in the body. A molecule or single unit of hemoglobin (Hb) contains 4 iron groups, each of which can bind 1 molecule or unit of oxygen. Because there are 4 iron groups, a molecule of Hb can contain from 0 to 4 molecules of O_2. Hb which is carrying O_2 is known as oxyhemoglobin (HbO_2), Hb not carrying oxygen in known as deoxyhemoglobin. The relative number of O_2 molecules bound to a Hb molecule is referred to as saturation, expressed in percentage. Of course, blood is composed of billions and billions of RBCs and Hb molecules, so the averaged saturation can take on any value from 0 to 100%.

How well Hb is saturated with O_2 depends mainly on the "partial pressure" of oxygen in the blood. The higher the pressure of oxygen in the blood (PO_2), the higher the saturation (SO_2). However, the relationship between PO_2 and SO_2 is not linear (change in one is not always directly proportional to change in the other). The dependence is described by a S-shaped "sigmoid" curve, common in the biologic sciences. This particular curve is call the Hemoglobin-Oxygen Dissociation Curve (HODC; see Figure 1). Hb absorbs O_2 in the lungs (to form HbO_2). As the RBC travels to the tissues, the HbO_2 releases oxygen.

Determination of the physiological parameters is a very important part of modern medical practice. Unfortunately, measurement of any of these parameters

has until recently always required a blood sample (arterial and/or venous) to be drawn, which is then analyzed by a laboratory.

During the 1970's the first pulse oximeter was introduced. This device made use of spectrophotometry to allow approximation of arterial oxygen saturation (SaO_2), termed SpO_2 (saturation measured by pulse oximetry), by noninvasive means. After improvements, pulse oximeters are now commonplace in acute health care settings.

Pulse oximeter design and function are well documented. The two principal forms of Hb (oxy and deoxy: Hb and HbO_2) absorb different wavelengths of light to varying degrees. The standard oximeter utilizes 2 wavelengths, one in the "red" portion of the light spectrum and the other in the near-infrared. The absorbance of emissions from light-emitting diodes (LEDs) of appropriate wavelength is measured. The pulsatile (AC) and non-pulsatile (DC) components are calculated and compared, and the ratio of the corrected signal is collated to a stored calibration curve to yield SpO_2.

Transcutaneous monitoring of oxygen and carbon dioxide is also used as discussed in S.J. Barker, "Monitoring Oxygen and Carbon Dioxide"; International Anesthesia Research Society, March 1996, pp 1-7, but there are several practical difficulties with this technology. It is dependent upon cardiac output and skin perfusion, the electrode must be calibrated before application to the skin, and the sensor's membrane and electrolyte must be replaced periodically. The only significant application has been found in neonatology.

There are many references disclosing noninvasive determination of glucose. However, no device has yet found acceptance in the marketplace for this function.

There have also been numerous attempts at monitoring using miniaturized probes passed through arterial cannulae. The first approach employed Clark electrodes, the same oxygen electrode used In the laboratory blood-gas analyzer. More recently, the principle of florescence quenching has been used to develop fiberoptic "optodes" which can continuously monitor pH and PCO_2 as well as PO_2 through an arterial cannula. Unfortunately, there have been some technical problems with optode accuracy and reliability. While this technology will no doubt improve, it remains very costly and is of course invasive in nature.

Thus, the SO_2 can now be determined noninvasively. However, still the only way to determine pH and other parameters accurately has been by drawing a blood sample and utilizing laboratory analysis. Such analysis is obviously invasive (requires breaking the skin; any time the skin barrier is ruptured inflammation and/or infection can ensue), very painful (puncture of an artery is technically more difficult and much more painful than puncture of a vein, which is how most blood tests are performed), risks blood contamination for both the subject and the person drawing the blood, and creates toxic medical waste (syringe, needle, gloves, skin dressing, test tube or other container). It is expensive to perform, not only from the supplies and the cost of the analyzer making the measurement, but the operation of the analyzer and the drawing of the blood both require trained personnel. The analyzer must be calibrated frequently with chemical reagents which are costly and must be disposed of safely. Arterial puncture is also inherently dangerous, as it can cause a clot in the artery, and prevent blood flow "downstream", thus depriving those tissues of oxygen.

Therefore, it would be an advance in the art to provide a system and method to noninvasively and quantitatively assess acid-base balance and related variables. It would be another advance in the art to noninvasively and quantitatively measure hemoglobin level ("blood count") and oxygen content and capacity. It would be yet another improvement in the art to determine all these parameters rapidly and continuously. It would be of great betterment to make these measurements without the need for laboratory analysis, equipment, and personnel. It would be an progression to have a device with such capabilities that is easily transportable that could be used in an ambulance or when conveying a patient from one location to another.

It would be a further advance to have a device for immediate diagnosis of poisoning such as that due to carbon monoxide. It would be advantageous to allow rapid noninvasive screening of blood disorders such as sickle cell anemia.

DISCLOSURE OF INVENTION

The subject invention concerns a novel method for noninvasive determination of proper of subject matter and the environment or milieu in which the subject matte ists. The method utilizes changes in molecules

induced by thermal energy to facilitate measurements. In a preferred embodiment, a new and unique method and device for noninvasive determination of oxygen saturation (SO_2), partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (PCO_2), bicarbonate ion (HCO_3^-), total carbon dioxide (TCO_2), acid-base balance (pH), base excess, total hemoglobin level (Thb), hematocrit (Hct) oxyhemoglobin level, deoxyhemoglobin level, and oxygen content is described.

The HODC is "shifted" to the left or right (as shown in Figures 2 and 3 and as discussed in the literature) by three factors: temperature, acid-base balance of the blood, and the concentration of substances called organic phosphates in the blood. The organic phosphates (the principal one is called 2,3-diphosphoglycerate: 2,3-DPG or 2,3-biphosphoglycerate: 2,3-BPG) are molecules which bind to Hb to facilitate oxygen transport. While they are important, disorders are very rare, and virtually all people can be assumed to have normal levels except in exceptional circumstances. They will not be addressed further here.

This leaves temperature and acid-base balance. The effects of these factors have been well described in the references cited. However, the only use of this information has been to "correct" values of blood samples to what they would read at standard temperature and pH.

The technology described herein utilizes the known shifts in the HODC, along with other science, to perform the measurements and calculations necessary to determine all parameters mentioned above. As mentioned, the factors which cause these shifts are well documented, as are the relative degrees of shift due to each factor. By controlling and varying temperature, one can calculate the degree of shift due to thermal effects. Any remaining degree of shift is due to alteration in acid-base balance. As the influence of acid-base balance upon the HODC is known, alterations and status of acid-base balance can be determined.

The oximeter estimates the SO_2 of blood. Thus, it is in effect delineating a point on the HODC. Clearly, this is oblivious of any shift in the curve. By measuring SO_2 at two or more points at known temperatures, or one point where the temperature is changed to two or more different known values, one can calculate the "standard" curve. Any deviation in measured values from this curve

imply an alteration in acid-base status.

In addition, the pH and PCO_2 are known to be affected by the temperature of blood, and these effects are quantified in the literature. (See, O.Siggaard-Anderson, The Acid-Base Status of the Blood, 4th Edition, pp. 29-91; Baltimore, MD; Williams & Wilkins (1974), and J.F. Nunn, Nunn's Appied Respiratory Physiology, 4th Edition, pp. 247-305; Cambridge, MA, Butterworth-Heinemann (1993).

Thus, comparison of saturation values at different known temperatures allows computation of acid-base balance and the parameters which affect it.

As the hemoglobin molecule is the primary buffer for acid-base balance in the body, estimation of hemoglobin level can be made from the degree of buffering effect (see Figure 4 and H.W. Davenport, The ABC of Acid-Base Chemistry, 5th Edition revised, pp. 8-68, Chicago, IL, University of Chicago Press (1971).

The technique of repetitious determinations made while altering temperature or other variables allows a multitude of additional analyses to be made. The determinations can be made intermittently or continuously.

The invention, together with additional features and advantages thereof, may best be understood by reference to the following description taken in connection with the accompanying illustrative drawings.

BRIEF SUMMARY OF DRAWINGS

Figure 1 is a representative graph of the normal hemoglobin-oxygen dissociation curve.

Figure 2 is a similar graph showing examples of "shifts" or alterations in the hemoglobin-oxygen dissociation curve due to changes in temperature.

Figure 3 is a similar graph showing examples of "shifts" or alterations in the hemoglobin-oxygen dissociation curve due to changes in acid-base (pH) status of the blood.

Figure 4 is a representative graph of the hemoglobin buffering effect in whole blood.

Figure 5a shows an embodiment of the invention for use on a finger. As mentioned in the text, any part of the body that can be successfully transilluminated with the radiant energy used can be utilized. Thus, toes, lips, etc.

could also be used.

Figure 5b shows an embodiment of the invention using two fingers.

Figure 5c shows an embodiment of the invention using three fingers.

Figure 6 shows a close-up of an embodiment of a probe for use on a finger. The temperature induction and measurement instrumentation are included, as are radiation emission and detection means. Information would be relayed between the probe and additional components (processing, entry, and display units).

Figure 7 shows an embodiment of the invention whereby fingers are placed inside a housing. This embodiment allows multiple simultaneous measurements to be made. The radiation source, emitters and detectors, and heating/cooling means would all be contained within the casing. The processing, entry, and display units could also be housed within the casing for a single self-contained assemblage.

Figure 8 shows a close-up of an embodiment of a casing containing elements of the invention.

Figure 9 shows a close-up of an embodiment of the invention for use on tubing.

Figure 10 shows a preferred embodiment for the production and transmission of light radiation. Light of a specific wavelength and intensity is generated and transmitted to the desired site.

Figure 11 shows a standard calibration curve used in pulse oximeters. The calibration curve is used by the oximeter to calculate arterial oxygen saturation (SaO_2) from the ratio (R) of the light absorbed (A) by the tissue being monitored.

MODE FOR CARRYING OUT THE INVENTION

Many forms of electromagnetic radiation can be used to aid in identification of, or to provide other relevant information about molecules, or substances, or their environment. The invention herein utilizes induced temperature changes to assist and improve these measurements, and enables determinations not previously possible. The description which follows is in reference to the study of blood , but can be applied to other substances as well.

All matter is affected by electromagnetic radiation and heating. The longer radio waves induce chiefly thermal agitation of molecules and excitation of

molecular rotations, while infrared rays excite vibrational modes of large molecules and release fluorescent emission as well as heat. These effects are documented in standard texts and reference works of physical chemistry. However, many biologic molecules, and a great number of other substances, exhibit effects or behavior when exposed to temperature variation which are not directly attributable to thermal energy. These indirect effects can be used to aid in identification of, or to provide other relevant information about, the molecule or substance or its environment. The invention herein detailed enables measurements and determinations of these effects. The description which follows is in reference to study of the hemoglobin molecule, but extension to other substances ensues clearly.

One part of the invention consists of methods of spectrophotometry and oximetry commonly employed in the practice of medicine. Another part of the invention consists of a device used to induce temperature changes in blood or other media. Included herein are algorithms for the calculation of variables not measured directly. The algorithm outlined below serves as an example, but modifications are possible to arrive at the indicated results, and are meant to be included within the spirit or this invention. In a preferred embodiment, the invention consists of a radiation delivery device 10 for facilitating the noninvasive monitoring of a characteristic of a patient's blood parameters. The device 10 as shown in Figures 5a-c and 6 is used to induce temperature changes in the blood. The device 10 includes a radiation emitter 12 having at least one wavelength being applied through a patient's tissue (T) to the patient's blood; a radiation detector 14 which detects reception of the at least one wavelength after absorbance through the blood; a temperature induction generator 16 for inducing temperature changes in the blood; and a controller 18 for computing the various blood parameters based on the absorbance of the at least one wavelength of radiation at various temperature levels of the blood. The radiation emitter 12, detector 14, temperature induction generator 16 are all inserted in a probe 20 which can be placed about the tissue/blood to be measured.

The probe 20 may also include a temperature sensing or measuring device 22 so that the temperature of the tissue and blood can be accurately determined. The controller 18 includes a computing device or standard personal computer (PC) with a monitor 24. Included within the controller are algorithms for the calculation

of variables not measured directly. The algorithm outlined below serves as an example, but modifications are possible to arrive at the indicated results, and are meant to be included within the spirit of this application. Various additional components of the device 10 will be discussed in more detail below with reference to Examples 1-18.

The normal temperature of the human body is defined to be 37^0 centigrade, the normal pH is defined to be 7.40, and the normal base excess is defined to be 0. These values are not necessary for the practice of the invention, but serve as reference points for values in the current medical literature.

Of note, the hemoglobin level and oxygenation of the blood in the arterial circulation is the same no matter where measured, as blood is thoroughly mixed in the left heart before ejection. Thus, the probes could be on fingers, toes, lips, etc., or any combination of these.

The description is also intended to include in vitro blood containers such as tubes 30 such as shown in Figure 9. The reference numerals in Figure 9 are the same as shown in Figure 6.

The electromagnetic radiation in this description will refer to light in the visible and infrared range although, as noted in the attached claims, it is conceivable that other forms could be used.

Similarly, while the present invention describes the use of transillumination, it will be appreciated that reflectance spectrophotometry may alternatively be employed.

The absorbance spectra for a great many substances are known, for example, that of glucose. A problem with infrared detection of glucose is that many other substances in blood have similar absorbances in regions of the infrared spectrum. This makes it difficult to differentiate glucose from these other substances. However, all infrared spectra will alter in response to temperature change. By definition, the spectra of different substances will change in different ways, because their molecular configurations are different. Thus, comparison or spectra at varying temperatures will allow separate identification.

OPERATION OF DEVICE

Incident radiation passing through a body part is attenuated (absorbed) in the tissue. The theoretical basis for spectrophotometric techniques is Beer's law

(the Beer-Lambert-Bouguer law) which expresses the incident intensity in terms of transmitted intensity and extinction coefficients of the tissue compartments through which the radiation has passed. The equation can be written as:

$$\ln(I_o/I)=ECL$$

where I_o is the incident intensity of the source radiation, I is the transmitted intensity of the source through the sample, E is the extinction coefficient of the component of interest, C is the concentration of the component in the tissue itself, and L is the optical path length (distance) through the absorber. Beer's law and the practice of spectrophotometry and oximetry have been exhaustively reviewed in the literature. Pulse oximetry in effect filters out signals other that pulsating (AC). In the body, it can be assumed that the pulsatile component of the signal is arterial blood, while all other tissue absorbers should be non-pulsatile (DC).

A light signal of a known intensity and wavelength is produced by means of light-emitting diodes (LEDs) as in currently used oximeters or, as in the preferred embodiment, a broad-band light source whereby wavelengths are isolated by a rotating filter or diffusion grating. In the latter case, the emitted light is distilled through a filter which allows a known wavelength and intensity of light to penetrate. Use of tunable lasers or other equipment is also possible.

If the light source is proximate to the point of use, no further mode of transmission will be needed. If it is not, the light will be transported to the desired point by means such as a fiber optic cable, preserving the wavelength and intensity.

Several means of temperature induction are possible. Possibilities are convection, conduction from gas or liquid, or radiant energy such as microwaves. As with the light signal, If the heating/cooling source is at or immediately adjacent to the area of need, no further transmission may be needed. If this is not the case, the means will be transported to the desired point by appropriate tubing or cabling.

Various means of temperature measurement are also possible. A large variety of electronic thermistors are commonly available. Other means such as infrared determination may also be used.

A broad-band photo detector (in the case of visible or infrared light) or other means will be utilized to measure the quantity of transmitted light. The wavelength, intensity, and timing of the emitted signal is known, allowing the

extinction coefficients for the compartments through which the light passed to be calculated.

To generate a single data point, the temperature induction means is used to bring the finger (or tubing or other space of interest) to a known temperature; a temperature measurement means will be used to confirm the temperature and adjust the temperature induction means if necessary. Light of known wavelength and intensity is emitted (and transmitted if necessary) on the surface of interest. Detection of the light signal at a distinct point (normally opposing surface) is made and the relative absorbance and extinction of the signal is calculated. This measurement may be repeated one or more times to ensure the accuracy of the measurement; this can be done within a very short time frame (less than a millisecond).

To generate multiple data points, the process outlined in the previous step will be repeated at the next chosen wavelength, while still at the same predetermined temperature. In the embodiment described herein, as shown in Figure 10, the filter 42 would be rotated so that the next wavelength filter would be adjacent to the fiber optic transmission cable. The range and number of wavelengths can be selected, and changed for different applications.

Once the desired number of wavelengths has been examined, the temperature induction means would bring the volume to a predetermined second temperature, and the data collection of steps would be repeated. At the completion of measurements and determinations for this second temperature, the temperature induction means will bring the space to a third predetermined temperature, and the measurements and determinations repeated. This process would be continued until the desired range of temperatures has been scrutinized.

The device can be operated intermittently or continuously. In the intermittent mode, a single set of calculations can be used for analysis to produce the determinations claimed. However, the device can also be easily operated in continuous mode, with the process outlined above repeated as often as wished (constantly if desired). In addition, a rapid ("stat") mode can be offered with the minimum number of measurements made that will provide an accurate estimation of correct values. Such a rapid mode would be useful in emergency situations.

While this methodology should give precise values, further adjustment may be desired to compensate for any discrepancies between theoretical and in vivo

measurements. Contemporary oximeters in fact use a calibration curve when determining oxygen saturation, with the curve being generated with data from normal volunteers. A standard calibration curve for a typical oximeter is shown in Figure 11. If necessary, such a calibration or compensation curve can be created for use with these procedures for performing noninvasive.

CALCULATIONS AND ANALYSIS

The "Henderson-Hasselbach" equation, which is discussed by A. Maas, et. al,"On the reliability of the Henderson - Hasselbalch equation in routine clinical acid - base chemistry", Annals of Clinical Biochemistry, Vol. 21, pp 26-39 (1984) is well known in physiologic chemistry, describes the dissolution of an acid in terms of pH, pK (dissolution or dissociation constant), and the concentrations of the acid and its salt or base. The solubility, α, of carbon dioxide (CO_2) is temperature-dependent, and the pK for CO_2 depends on both temperature and pH. For CO_2, the Henderson-Hasselbach equation becomes:

$$pH = pK + \log \frac{[HCO_3^-]}{\alpha\, PCO_2};$$

or an alternate form can be used:

since $[TCO_2]$ is very close to the sum of $[HCO_3^-]$ and $\alpha\, PCO_2$,

$[TCO_2] = [HCO_3^-] + \alpha\, PCO_2$ and

$[HCO_3^-] = [TCO_2] - \alpha\, PCO_2$; then

$$pH = pK + \log \frac{[TCO_2] - \alpha\, PCO_2}{\alpha\, PCO_2}$$

The degree of shift of the HODC is determined using calculations similar to that described below by Nunn (referenced above) and Kelman (G.R. Kelman, "Nomograms for Correction of Blood PO_2, PCO_2, pH, and Base Excess for Time and Temperature", Journal of Applied Physiology, Vol. 21, No. 5. pp 1484 - 1490, (1966)), and modified by Siggaard-Andersen (referenced above) and others, can be calculated by:

temperature factor = antilog{0.024(37-temperature)}

pH factor = antilog{0.48(pH-7.40)}

base excess factor = antilog{-0.0013 x base excess}

Calculation of blood oxygen content is made by computations similar to that of Nunn:

content (ml O_2/dl) = THb(g/dl) x SO_2 x 1.38(ml O_2/g HbO_2) + 0.003 x PO_2

Conversion of PO_2 to SO_2 is done using modifications of Adair's equation or Kelman's computation:

$$SO_2 = (25 \times (0.0257 \times PO_2 + 2 \times 0.00078 \times (PO_2)^2 + 3 \times 0.00000444 \times (PO_2)^3 + 4 \times 0.00000255 \times (PO_2)^4) / (1 + 0.0257 \times PO_2 + 0.00078 \times (PO_2)^2 + 0.00000444 \times (PO_2)^3 + 0.00000255 \times (PO_2)^4))$$

calculation of base excess can be done by the following formula or other known means:

$$\text{base excess} = (1 - 0.0143 \times Hb) \times ([HCO_3^-] - 24)$$

It should be noted that all stated formulas are subject to change and/or modification, and represent approximate values. Alterations of this algorithm will be suggested to those skilled in the art, and are meant to be included within the scope and spirit of this application.

The following algorithm describes the use of the present invention. Some variables have degrees of co-dependence. In these cases, values are calculated by iterative computational techniques.

Measurement of SO_2 is made by a first probe 12 and apparatus 10 comparable to that shown in Figures 5 and 6, using methods similar to standard oximetry described in the prior art. The probe is at a set known temperature. Calculation of PO_2 is made using computations similar to those described in the references and set forth above. For convenience, this probe may be brought to 37°, in which case the "true PO_2" can be calculated without correction for temperature ("normalization" to 37°). If the temperature is in fact a different value,

correction may made by methods similar to those described in the references and described above.

Measurement of SO_2 is made by a second probe at a different temperature. Alternately, the temperature of the single probe can be changed, and a determination of SO_2 made at the new temperature. A higher or lower value of temperature can be used, although for ease of measurement one may be preferable.

Calculation of PO_2 is made as above. The difference in PO_2 due to the temperature difference (shift in HODC) between the two measurements is factored.

After the temperature change has been factored, any remaining difference is due to a shift in the HODC due to acid-base balance. This is primarily due to pH and only a very small component is due to base excess. The base excess can be computed by other means and then back-factored into the calculated shift in the HODC.

The "pH factor" is calculated from the ratio of the two determinations of PO_2.

Correction of the pH factor is made for the known change in pH due to change in temperature. Biochemically, temperature has an effect on the hydrogen ion distinct from the shift in the HODC.

The alteration of pH from normal (7.40) is calculated. If there is no alteration, this implies a pH of 7.40.

Now that the pH is known, computation of the carbon dioxide parameters is done using the Henderson-Hasselbach equation as described above. The effect of temperature on PCO_2 is known, as in the consequence of temperature and pH on pK. Thus, PCO_2, $[HCO_3^-]$, and $[TCO_2]$ can be computed or calculated by nomograms similar to those elucidated by Siggaard-Andersen (referenced above) and others.

Now that the pH and $[HCO_3$-] are known, computation of Hb level can be made by construction of the buffer line of blood as shown in Figure 4 (see also, Davenport, referenced above). Calculation of base excess is done as in the formula above. As mentioned, base excess can also be computed from a relative shift in the HODC, and this additional computation can serve as a confirmation of

Hb level.

Oxygen content is computed as per the calculation above.

As mentioned above, modifications of this algorithm will be suggested to those skilled in the art, and are meant to be included within the scope and spirit of this application. For instance, the case of base excess was cited. Additionally, the effects of 2,3-DPG have been ignored in this description, as they are not normally considered in current clinical practice. Clearly one may wish to take these into account under certain circumstances.

Similarly, the effects oxygen and carbon dioxide have on the transport of each other in blood are described by the Bohr and Haldane effects (together with hemoglobin level). These effects can be used to calibrate and validate results.

Following are examples which illustrate procedures for practicing the invention. These should not be construed as limiting, and that various modifications will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims.

EXAMPLE 1

A single probe 20 similar to that illustrated in Figures 5a and 6 is used. Measurement of SO_2 is made by use of a light signal 12 and photo detector 14. The heating/cooling element 16 in the probe 20 is then used to raise the temperature of the finger (F) to approximately 40^0 C A second measurement of SO_2 then is made. The algorithm outlined above is used by a computing device 18 to calculate all relevant variables which can be displayed on a monitor 24 for evaluation by a user.

A device 10 such as this might be used in place of laboratory analysis for stable patients or part of routine physical diagnosis, where the parameters are expected to change very little over the course of several minutes.

EXAMPLE 2

Two probes 26 and 28 similar to that illustrated in Figure 5b are used. The heating/cooling element 16 in one of the probes is used to raise the temperature of its finger to approximately 40^0 C. Simultaneous measurements of SO_2 are made

by the two probes, one probe at body temperature and the other probe at the raised temperature. The algorithm outlined above is used to calculate all relevant variables.

Alternatively, the embodiment shown in Figures 7 and 8 is used. A device 40 such as this might be used during anesthesia for brief or low-risk surgery, where the parameters might be expected to change somewhat over the course of several minutes. The device 40 is provided with a hand and finger housing 42 which receives several fingers of a human patient within the housing. A single or multiple probes similar to that shown in Figure 6 can be provided in the housing with respective heating/cooling elements.

EXAMPLE 3

Three probes 32, 34, and 36 similar to that illustrated in Figure 5c are used. A first probe 32 is used without heating or cooling the respective finger. The heating/cooling device 16 in a second probe 34 is used to raise the temperature of one finger to approximately 40^0 C. The heating/cooling device 16 in a third probe 36 is used to lower the temperature of a respective third finger to approximately 33^0 C. Simultaneous measurements of SO_2 are made by the three probes 32, 34, and 36. The algorithm outlined above is used by a computing device to calculate all relevant variables.

Alternatively, the embodiment shown in Figures 7 and 8 having multiple finger probes could be used.

A device such as this might be used in emergency rooms, critical care units, or during anesthesia for high-risk patients, where there is concern that the determined parameters might change very rapidly, and also where significantly lower values of SO_2 and PO_2 may occur.

EXAMPLE 4

Two probes 20 similar to that illustrated in Figure 9 are used. The heating/cooling device 16 in one of the probes is used to raise the temperature of its tubing 30 and contents to approximately 40^0 C. Simultaneous measurements of SO_2 are made by the two probes. The algorithm outlined above is used to calculate all relevant variables.

A device such as this might be used during hemodialysis, where the blood is circulated in tubing outside the body, and parameters might expected to change over the course of several minutes.

EXAMPLE 5

Three probes 20 similar to that illustrated in Figure 9 are used. The heating/cooling devices 16 in the probes are used to bring the temperatures of three separated pieces of tubing 30 and their contents to 33°, 37°, and 40°, respectively. Simultaneous measurements of SO_2 are made by the three probes. The algorithm outlined above is used to calculate all relevant variables.

A device such as this might be used during cardiopulmonary bypass, where the blood is circulated in tubing outside the body, and parameters might be expected to change rapidly.

EXAMPLE 6

A single probe 20 similar to that illustrated in Figures 5a and 6 is used. The heating/cooling device 16 in the probe is used to vary the temperature of the finger from 33° C to 40° C in increments of 1° C. Measurements of SO_2 are made at the differing temperatures. The algorithm outlined above is used to calculate all relevant variables.

In this manner, a series of data is collected for improved accuracy in performing calculations.

Comparably, an example with a single probe 20 for tubing 30 similar to that in Figure 9 is envisioned.

EXAMPLE 7

Two or more probes 20 similar to that illustrated in Figures 5a and 6 is used. The heating/cooling device 16 in the probes are used to vary the temperatures of the fingers from 33° C to 40° C in increments of 1° C. Measurements of SO_2 are made at the differing temperatures. The algorithm outlined above is used to calculate all relevant variables.

In this manner, a series of data is collected for improved accuracy in performing the calculations.

Comparably, an example with two or more probes 20 for tubing 30 similar to that in Figure 9 is envisioned.

EXAMPLE 8

A single probe similar to that illustrated in Figures 5a, 5b, 5c, and 6 are used. Absorbance of emitted radiation over several wavelengths is measured.

A device such as this might be used to measure glucose, potassium, urea, creatinine, or other blood constituents. It could also detect substances not normally present in blood (or present in very small quantities) such as fetal hemoglobin, myoglobin, etc.

Comparably, examples with two or more probes for tissue or tubing are envisioned.

It is clear from the prior art cited that the invention described herein will measure the presence of other substances in blood in a manner equal, and in many cases superior, to current techniques.

EXAMPLE 9

A single probe 20 similar to that illustrated in Figure 9 is used. Instead of blood, measurements are made from a different body fluid such as urine, using the tubing from a bladder catheter.

A device such as this might be used to measure glucose, urea, creatinine, or the excretion of some substance in the urine

Comparably, examples with two or more probes 20 for tissue (T) or tubing 30 can be utilized as discussed above.

EXAMPLE 10

A single probe 20 similar to that illustrated in Figures 5a and 6 is used. A multitude of wavelengths is scanned. Detection of ingested drugs, medications, or other substances, or their metabolites, is made. Similarly, substances which appear within the body after other types of exposure, such as inhalation, can be measured.

Comparably, examples with two or more probes 20 for tissue (T) or tubing 30 can be utilized.

A device of this nature mav be used in the workplace. hospital emergencv

rooms, or laboratories. Diagnosis of carbon monoxide poisoning (carboxyhemoglobin level) will be made rapidly and noninvasively. Even more importantly, the consequences of this poisoning, in the form of reduction in oxygen carrying capacity and metabolic acidosis, will be quickly known, allowing appropriate therapy to be chosen (oxyhemoglobin, carboxyhemoglobin, oxygen content, and pH can all be measured with the present invention). The results of therapy can be monitored continuously, and as long as necessary.

EXAMPLE 11

A single probe 20 similar to that illustrated in Figures 5a and 6 is used. A multitude of wavelengths is scanned. Screening of sickle cell disease or trait or other hemoglobinopathies can be done quickly and noninvasively for large populations. Results can be confirmed by traditional laboratory analysis.

Comparably, examples with two or more probes 20 for tissue (T) or tubing 30 can also be utilized.

It is within the scope of this invention for diagnosis of other diseases or conditions which can be distinguished by markers in blood or other substances carried in blood or other body fluids. Examples include blood typing, screening of potential donors for bone marrow transplantation, certain cancers, etc.

EXAMPLE 12

Emitters and detectors can be arranged in serial pairs or a like configuration in probes similar to those in Figures 5 and 6. This would enable calculations made in the time or frequency domain, such a wave or pulse velocity. Emitters and detectors can be also grouped in parallel or concentric arrangement in probes similar to those in Figures 5 and 6. This would enable multi-dimensional analysis, comparable to computerized tomography.

EXAMPLE 13

The use of the present invention in monitoring of water or other liquids is also envisioned. A mechanism could be easily constructed whereby a modification of the invention could be placed "in-line" for the water system of a building or city. In this manner the quality and purity of the water are constantly

monitored and protected. The light absorption characteristics of an enormous number of substances are known, and can thus be screened for by the method of the present invention. Toxins, contaminants, or undesired substances can be detected and recognized quickly and easily, and appropriate measures instituted.

The sampling would not in any way affect the water or liquid, and the fluid would never leave its existing containers, such that samples would not have to be collected or disposed of in environmentally safe methods..

EXAMPLE 14

The use in monitoring of air or other gases is also envisioned. A mechanism in which samples of air from a building or industrial plant are continually monitored. As mentioned in the previous example, the light absorption characteristics of a large number of substances are well documented, and these elements can be detected using this technique. Air quality can be monitored on a constant basis. Atmospheric sampling can be performed.

EXAMPLE 15

The in vitro utilization of this invention is further envisioned. Samples of blood or other body fluids can be taken, stored, and analyzed using the device at a later point. While some characteristics of blood or biologic fluids change over time, these changes are also well known, and the original characteristics can often be inferred.

In the same line of reasoning, the invention may be used to investigate changes and alterations in blood or other substances over time or after subjecting the blood or other substance to some intervention. This is because the invention is noninvasive and nondestructive.

EXAMPLE 16

The use in remote sensing applications is possible. Infrared techniques for distant temperature sensing are in use. When combined with the present invention, one may be able to measure many biochemical processes remotely as well. This will assist in the study of atmospheric and other pollution, and a myriad of additional processes.

EXAMPLE 17

The use in environmental studies, such as the investigation of global warming, is foreseen. Substances are sought as markers which indicate temperature changes over a period of time. This invention will aid in this by identifying changes due to temperature.

EXAMPLE 18

A broad range of additional applications is envisioned. Ultraviolet and X-ray radiation are used in the technical analysis of artwork to assist in the establishment authenticity and age. Modifications of this invention will help in nondestructive testing by detection of substances within such works.

EXAMPLE 19

It is known that the infrared absorbance spectrum of water changes with temperature. The absorbance spectra of elements contained within water (contaminants, pollutants, or other substances) will also change with temperature. The spectra of these substances will change in a different manner than the spectrum of water. Thus, use of temperature pertubation or other agitation may greatly aid in analysis of such substances, without having to change the primary detection means. Many types of analysis tools and techniques currently in use could be greatly improved without large investment or retooling. Future analysis techniques could be developed utilizing this methodology to assist in measurements.

Other variables or parameters not mentioned above an also be measured or estimated. For example, the hematocrit is commonly estimated as three times the hemoglobin level. As the primary determinants of blood viscosity are temperature and hematocrit, this can be estimated, which allows additional calculations of pressure, vessel elasticity, etc.

The use of multiple or broad spectrum wavelength emission and detection (possibly combined with appropriate filters) enables the identification of a multitude of blood constituents, either naturally occurring or as the product of metabolism or pharmacokinetics. The identification of certain substances and their concentrations allows their use as references for determination of others.

Hemoglobins are found in all classes of vertebrates, in most invertebrate phyla, and even in some plants. Other respiratory pigments such as chlorocruorins, hemerythrins, and hemocyanins are found in other organisms. The function of all is dependent upon temperature and pH. Similarly, plants contain the molecule chorophyll in several forms. This substance is closely related to the hemoglobins of animal systems, and is also extremely sensitive to temperature changes. A multitude of other molecules, such as phosphorus compounds like the adenosine phosphates (ATP and others), found in both plants and animals, are reactive to temperature variation. The technology outlined in this patent application is relevant to measurements and determinations for all these substances and, in many cases, the environments or milieu in which they exist.

The technique may be utilized on homogeneous elements or matter which is a combination of substances.

It should be understood that the examples and embodiments described herein are for illustrative purposes only, and that various modifications and embodiments will be suggested to persons skilled in the art. The claims are meant to include all such modifications and embodiments.

DEVICE FOR NONINVASIVE DETERMINATION OF BLOOD PARAMETERS

CLAIMS

1. A radiation delivery device (10, 40) for facilitating the noninvasive monitoring of a characteristic of a patient's blood parameters, the device comprising:

a radiation emitter (12) having at least one wavelength being applied to the patient's blood;

a radiation detector (14) which detects reception of said at least one wavelength after absorbance through said blood;

a temperature induction generator (16) for inducing temperature changes in said blood; and

a controller (18) for computing the various blood parameters based on the absorbance of said at least one wavelength of radiation at various temperature levels of said blood.

2. The radiation delivery device (10. 40) of claim 1 wherein the radiation is selected from the group of visible light, infrared light, and ultraviolet light.

3. The radiation delivery device (10, 40) of claim 1 wherein the radiation emitter (12) has at least one wavelength being applied to a patient's tissue including blood, and said radiation detector (14) detects reception of said at least one wavelength after absorbance through said tissue.

4. The radiation delivery device (10, 40) of claim 3, wherein said tissue is selected from the group comprising hands, fingers, feet, toes, ears, earlobes, nares, lips, and tongue.

5. The radiation delivery device (10, 40) of claim 3, wherein the temperature induction generator (16) raises the temperature of the patient's tissue including blood.

6. The radiation delivery device (10, 40) of claim 5, wherein the temperature induction generator raises the temperature of the patient's tissue

including blood to about 40° c.

7. The radiation delivery device (10, 40) of claim 3, wherein the temperature induction generator (16) lowers the temperature of the patient's tissue including blood.

8. The radiation delivery device (10, 40) of claim 7, wherein the temperature induction generator (16) lowers the temperature of the patient's tissue including blood to about 33°C.

9. The radiation delivery device (10, 40) of claim 3, wherein the temperature induction generator (16) raises and lowers the temperature of the patient's tissue including blood; and

said controller (18) for computing the various blood parameters based on the absorbance of said at least one wavelength of radiation computes the various blood parameters at each of the lower, normal and higher temperature of said tissue including blood.

10. The radiation delivery device (10, 40) of claim 9, wherein the temperature levels are about 33, 37, and 40°, respectively.

11. The radiation delivery device (10, 40) of claim 1, wherein the patient's blood is carried in tubing (30), and the radiation emitter (12) is being applied to said tubing and contents, the radiation detector (14) is detecting through said tubing and contents, said temperature induction generator (16) is inducing temperature changes in said tubing and contents, and said controller (18) is computing the various blood parameters based on the absorbance of said at least one wavelength of radiation at various temperature levels of said tubing and contents.

12. A radiation delivery device (10, 40) of claim 11, where in the temperature induction generator (16) raises and lowers the temperature of the tubing and blood contents; and

the controller (18) for computing the various blood parameters measures

the absorbance of said radiation at the lower, normal and higher temperature of said tubing and blood contents.

13. A radiation delivery device (10,40) of claim 1, further comprising a plurality of radiation emitters (12), matching radiation detector (14) and generators (16), each matching emitter, detector and temperature induction generator being able to be set at different temperature levels so that said controller can simultaneously measure the absorbance of said radiation at said various temperature levels of said blood.

14. A device (10, 40) to detect and measure elements of the blood, including, but not limited to, hemoglobin in any of its forms, comprising

an emission means (12);

a detecting means (14) which detects reception of said emission means after contact with the blood;

means (16) of inducting a temperature change in the blood;

means (22) of measuring the temperature of the blood;

a controller means (18) for computing the various blood elements based on the contact of said radiation from said emissions means at various temperature levels of the blood, the controller having an input means (18) to allow various changes in the emission means, detecting means, and temperature inducting means;

and a display means (24) to relay the various blood elements to an end user of the device.

15. A device (10,40) of claim 14, wherein the detector means (14) detects the radiation emitted by said emission means (12).

16. A device (10,40) of claim 15, wherein the radiation emitted by said emission means (12) is selected from the group comprising visible light, infrared light, and ultraviolet light.

17. A device (10,40) of claim 15, wherein the means (16) of induction of temperature changes in said blood is selected from the group comprising

conduction, convection and radiation.

18. A device (10,40) of claim 14, wherein the means (22) to measure temperature of said blood is selected from the group comprising electronic, and infrared.

19. A device (10,40) of claim 14, further comprising of plurality of emission means (12), detection means (14), means (16) for induction of temperature, and means (22) for measuring temperature.

20. A method for noninvasively determining one or more of the following blood parameters; total hemoglobin, oxygen saturation, partial pressure of oxygen, partial pressure of carbon dioxide, bicarbonate ion, total carbon dioxide, acid-base balance, base excess, oxyhemoglobin, deoxyhemoglobin, and oxygen content, in an animal or human, said method comprising of steps of:

emitting radiation (12) having at least one wavelength to the blood;

detecting (14) said radiation having at least one wavelength after contact with the blood;

inducing (16) a temperature change in said blood while emitting and detecting said radiation through the blood; and

computing (18) the various blood parameters based on the contact of said at least one wavelength of radiation at various temperature levels of the blood.

21. The method of claim 20, wherein said detecting step (14) is selected from the group comprising detecting said radiation after absorbance, reflection, and any combination thereof with the blood.

22. The method of claim 20, wherein said radiation is selected from the group comprising visible light, infrared light, and ultraviolet light, or any combination thereof.

23. The method of claim 20, wherein the inducing (16) a temperature change step includes conduction, convection, and radiation or any combination thereof.

24. The method of claim 20, further including a step of measuring (22) the temperature of the blood.

25. The method of claim 20, wherein said emitting step (12) includes the emission of a plurality of wavelengths to the blood.

26. The method of claim 20, wherein said blood is contained in animal or human tissue and the radiation is being emitted to contact said tissue.

27. The method of claim 26, wherein said tissue is selected from the group comprising hands, feet, toes, ears, earlobes, nares, lips, and tongue.

28. The method of claim 20, wherein said blood is contained in a tube (30) outside of the animal or human tissue and the radiation is being emitted through said tube.

29. The method of claim 20, wherein the emitting step (12) includes a plurality of emitters (12) having at least one wavelength, and the detecting step (14) includes a plurality of detectors (14) for detecting the radiation from said emitters.

30. A device (10,40) for noninvasively determining characteristics of subject matter and the environment in which the subject matter exists, the device comprising:

an emitter means (12) having at least one wavelength of electromagnetic radiation applied to the subject matter;

a detector means (14) which senses and measures reception of said wavelength after contact with the subject matter;

a temperature induction means (16) for generating temperature changes in the subject matter; and

a controller (18) for manipulating said emitter means, detector means, and temperature inductors means and for computing parameters based on information processed from the contact of said radiation at various temperature levels on the subiect matter.

31. A device (10,40) of claim 30, wherein the subject matter is a living organism and the characteristics determined are the temperature induced changes in biologic molecules.

32. A device (10,40) of claim 30, wherein the detector means (14) senses and measures reception of said wavelength after absorbance through said subject matter.

33. A device (10,40) of claim 30, wherein the detector means (14) senses and measures reception of said wavelength after reflection from the subject matter.

34. A device (10,40) of claim 30, wherein the detector means (14) senses and measures reception of said wavelength after refractance from the subject matter.

35. The device (10,40) of claim 30, wherein the emitter means (12) and detector means (14) are arranged serially thereby allowing calculations in time and frequency parameters, such as velocity of wave and pulse flow.

36. The device (10,40) of claim 30, wherein the emitter means (12) and detector means (14) are arranged in a parallel manner, thereby allowing calculations in more than one physical dimension, such as amplitude.

37. A device (10,40) according to claim 30, utilizing induced changes in temperature to effect alterations in the hemoglobin-oxygen dissociation curve, for noninvasively determining one or more of the following blood parameters;

oxygen saturation, partial pressure of oxygen, partial pressure of carbon dioxide, concentration of bicarbonate ion and total carbon dioxide, acid-base balance, base excess, hemoglobin level, oxyhemoglobin level, deoxyhemoglobin level, and oxygen content.

38. A method for facilitating the noninvasive determination of characteristics of subiect matter and the environment in which said subiect matter

exists, the method comprising the steps of:

emitting (12) at least one wavelength of electromagnetic radiation applied to said subject matter

detecting (14) said wavelength(s) after contact with said subject matter;

inducing (16) a temperature change in said subject matter while emitting and detecting said radiation being applied to said subject matter; and

computing (18) parameters based on information processed from the contact of said radiation at various temperature levels on said subject matter.

39. The method of claim 38, wherein said detection step (14), is selected from the group comprising detecting said radiation after absorbance, reflection, and any combination thereof with the subject matter.

40. The method of claim 38, wherein the inducing (16) a temperature change step includes conduction, convection, and radiation or any combination thereof.

41. The method of claim 38, further including the step (22) of measuring the temperature of the subject matter.

42. The method of claim 38, wherein said emitting step (12) includes the emission of a plurality of wavelengths to the subject matter.

43. A method for determination of hemoglobin level by means of measuring hemoglobin buffering effect in blood, the method comprising the steps of:

determining the pH of the blood in accordance with the method of the present invention,

calculating the bicarbonate ion in accordance with the method of the present invention, and

estimating the hemoglobin buffering effect by comparing the pH and bicarbonate ion levels together, then computing the total hemoglobin level therefrom.

Figure 1

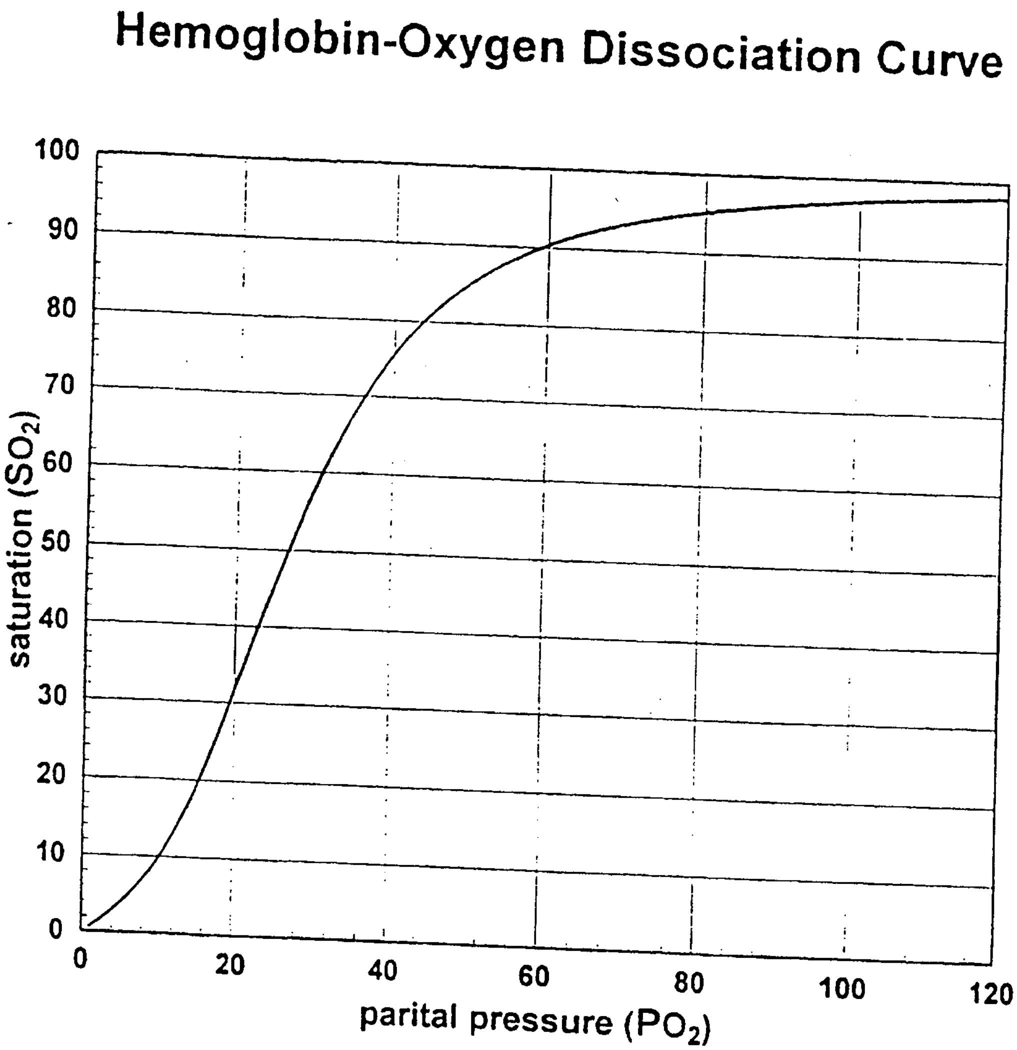

Hemoglobin-Oxygen Dissociation Curve
saturation (SO_2)
0
10
20
30
40
50
60
70
80
90
100
0
20
40
60
80
100
120
parital pressure (PO_2)

Figure 2

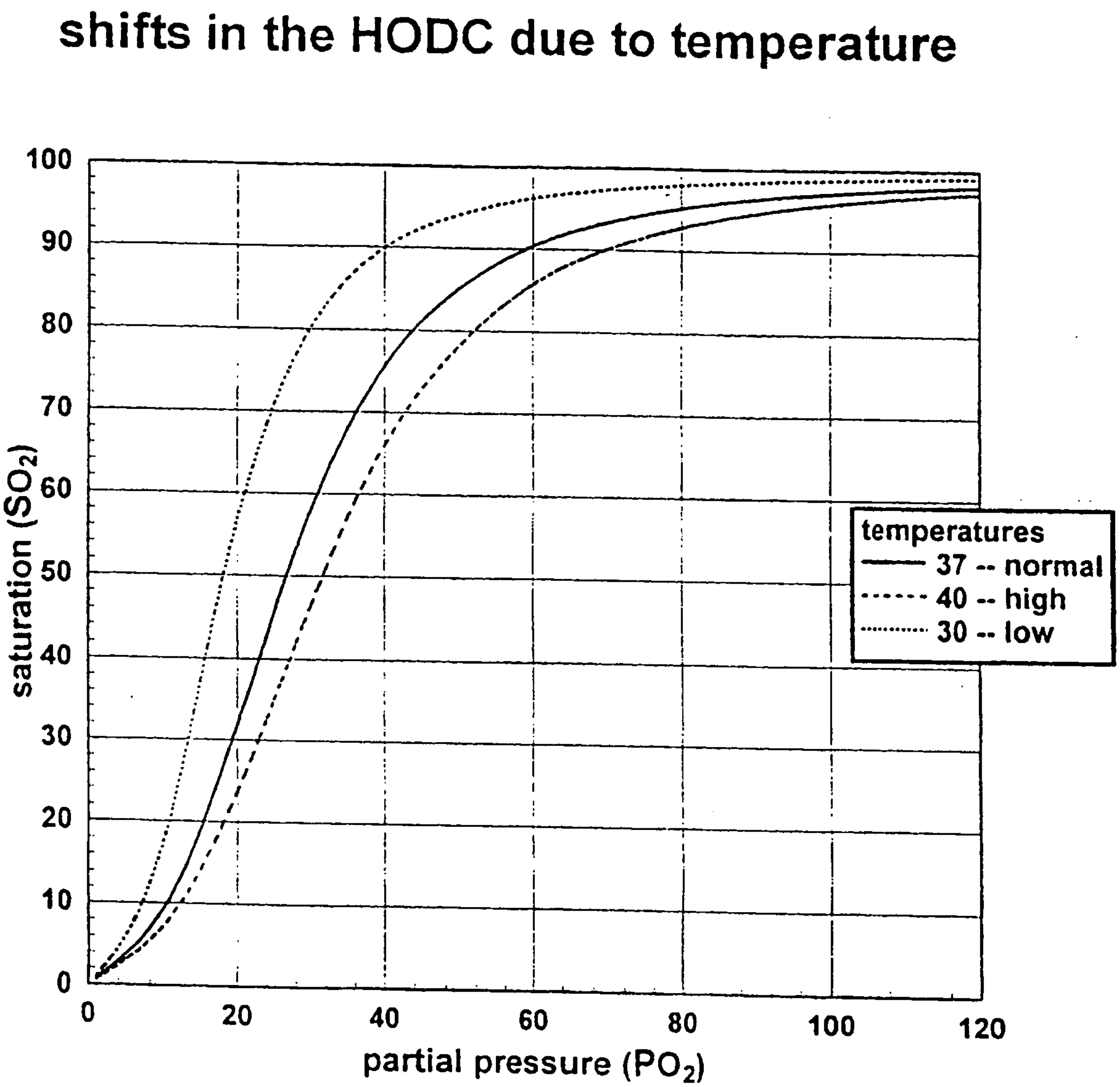

shifts in the HODC due to temperature
saturation (SO_2)
partial pressure (PO_2)
temperatures
37 -- normal
40 -- high
30 -- low
0
10
20
30
40
50
60
70
80
90
100
0
20
40
60
80
100
120

Figure 3

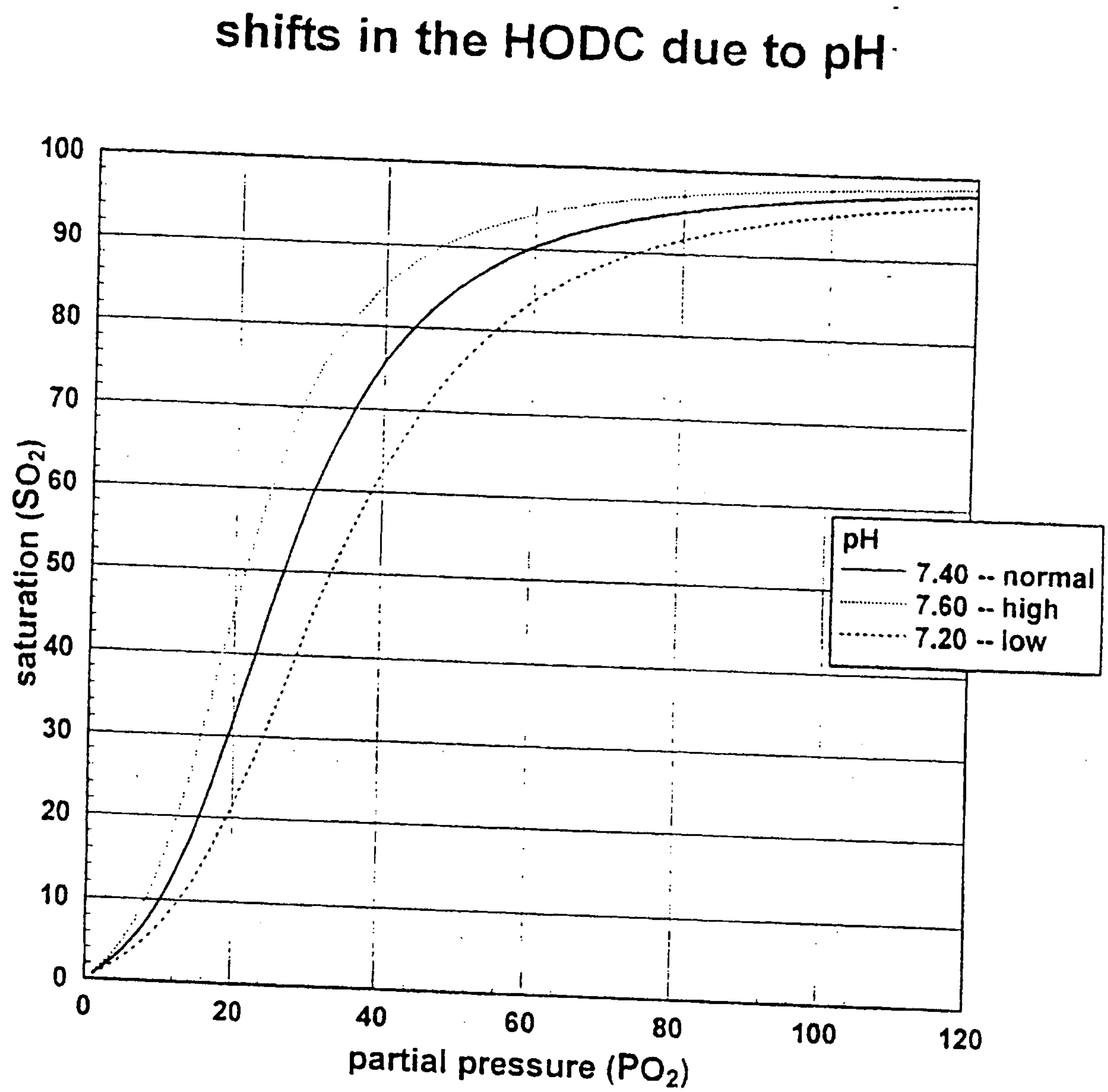

shifts in the HODC due to pH
saturation (SO_2)
partial pressure (PO_2)
0
10
20
30
40
50
60
70
80
90
100
120
pH
7.40 -- normal
7.60 -- high
7.20 -- low

Figure 4

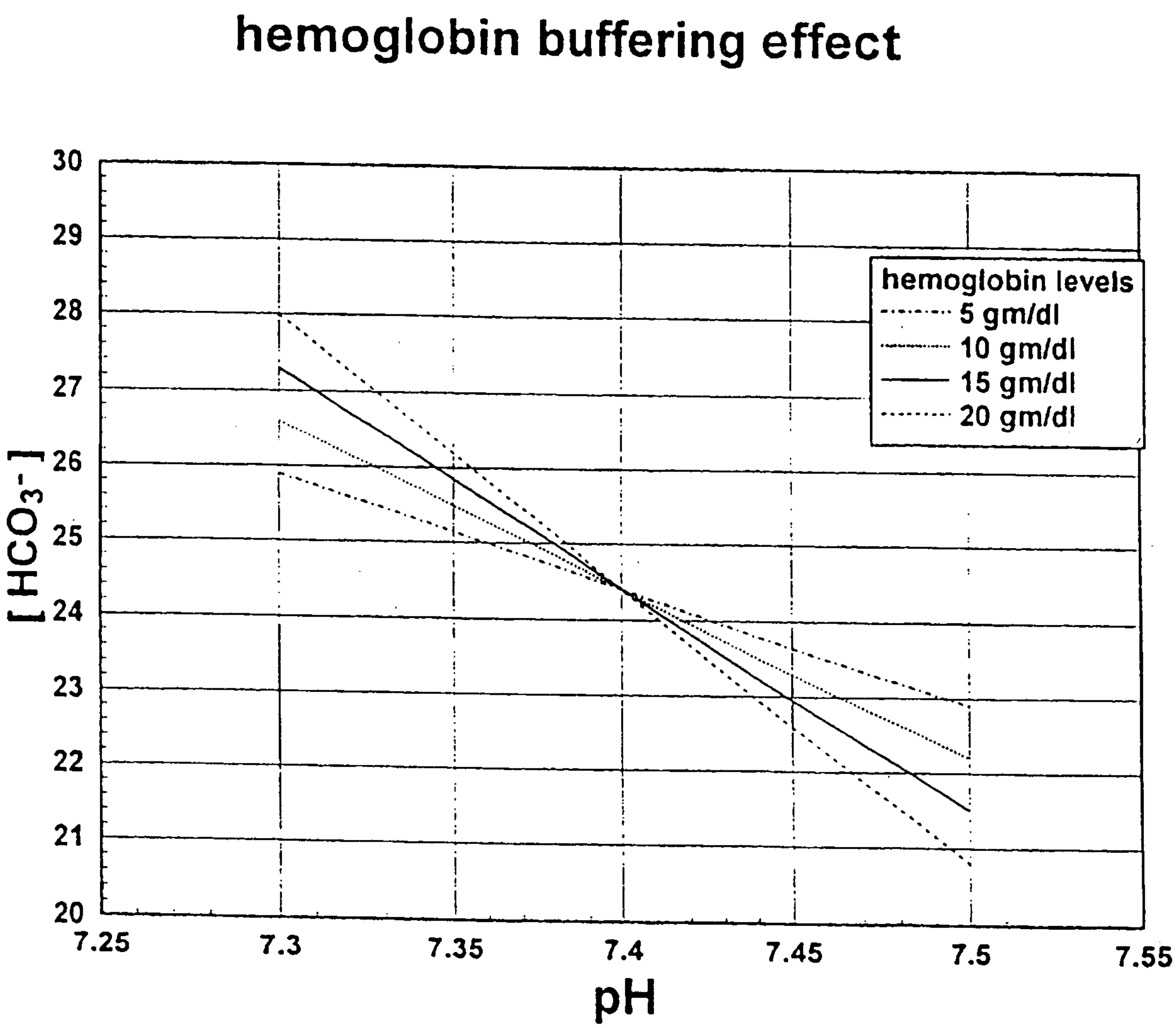

hemoglobin buffering effect
30
29
28
27
26
25
24
23
22
21
20
[HCO_3^-]
7.25
7.3
7.35
7.4
7.45
7.5
7.55
pH
hemoglobin levels
5 gm/dl
10 gm/dl
15 gm/dl
20 gm/dl

Figure 5a

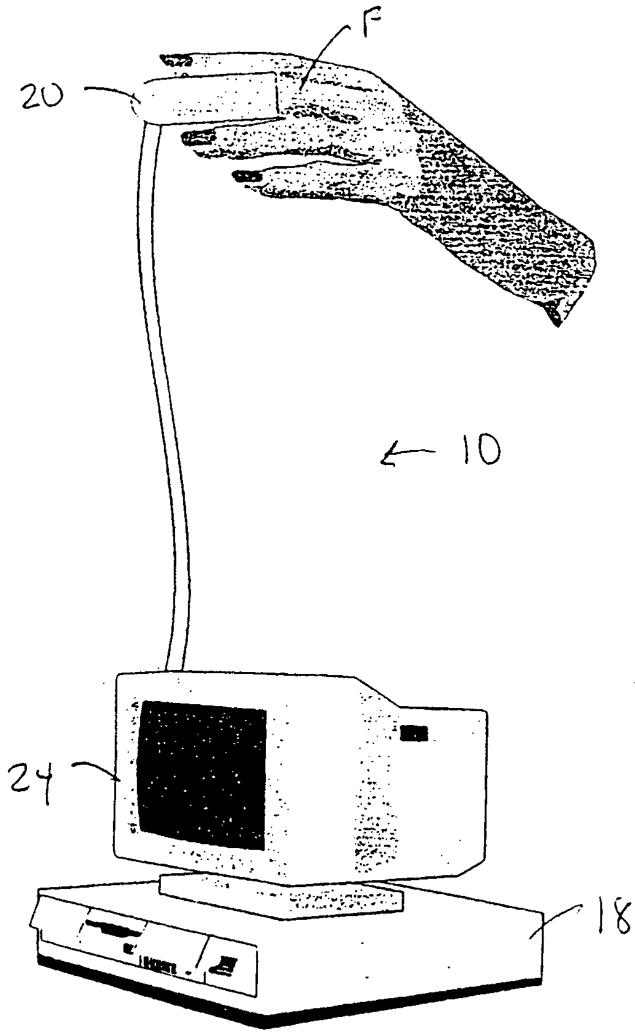


Figure 5b

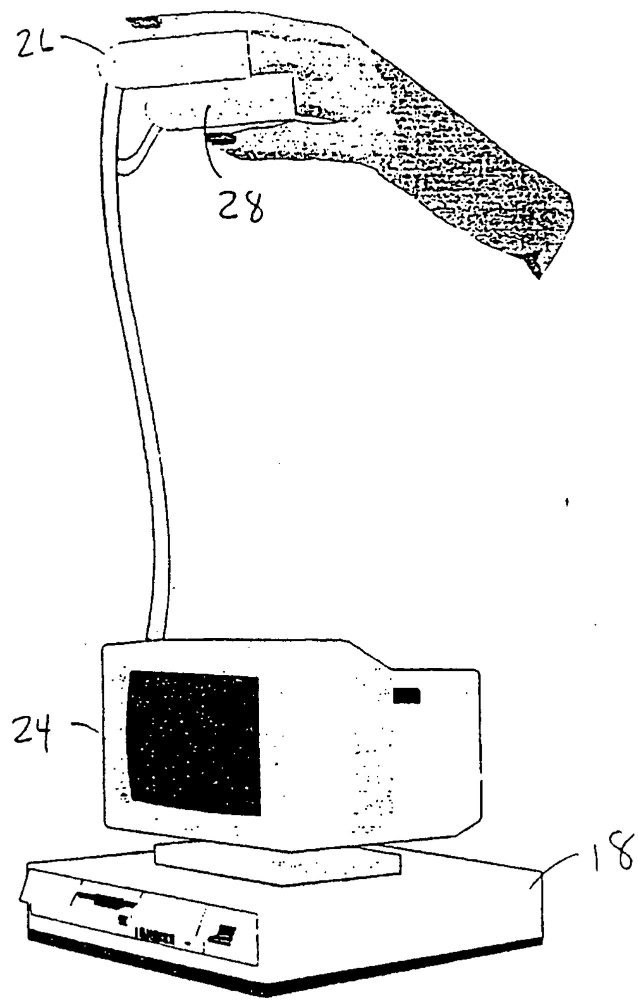


Figure 5c

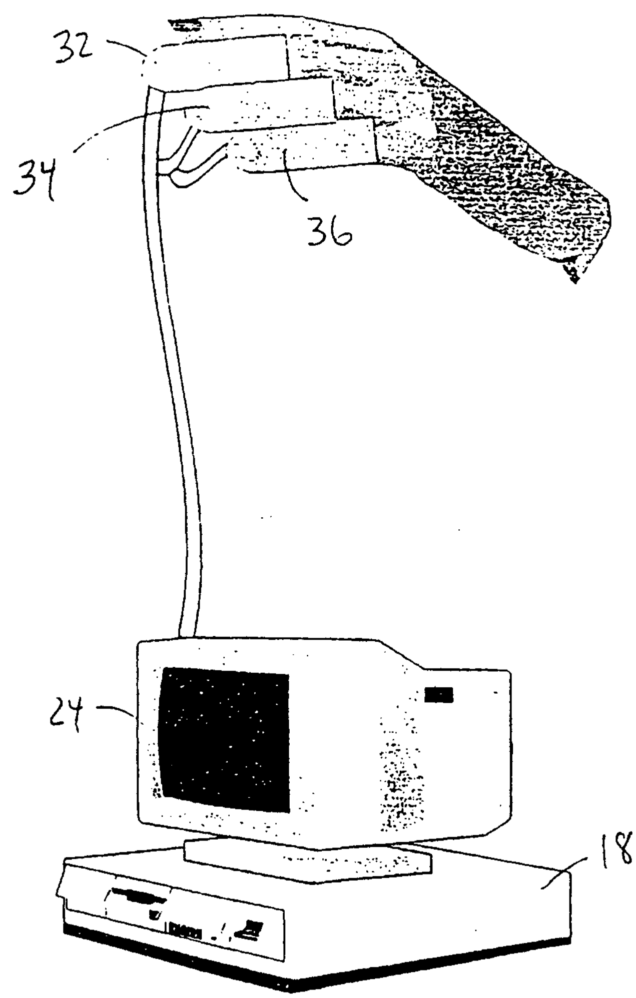


Figure 6

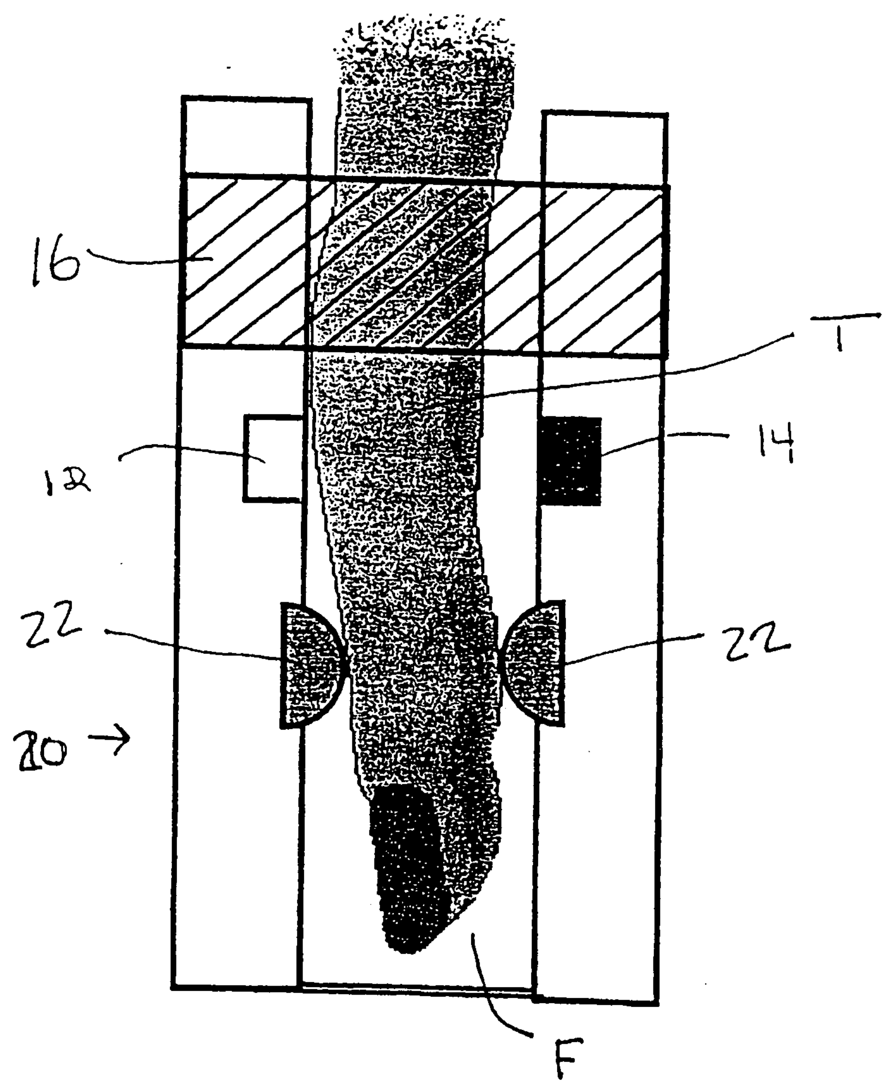


Figure 7

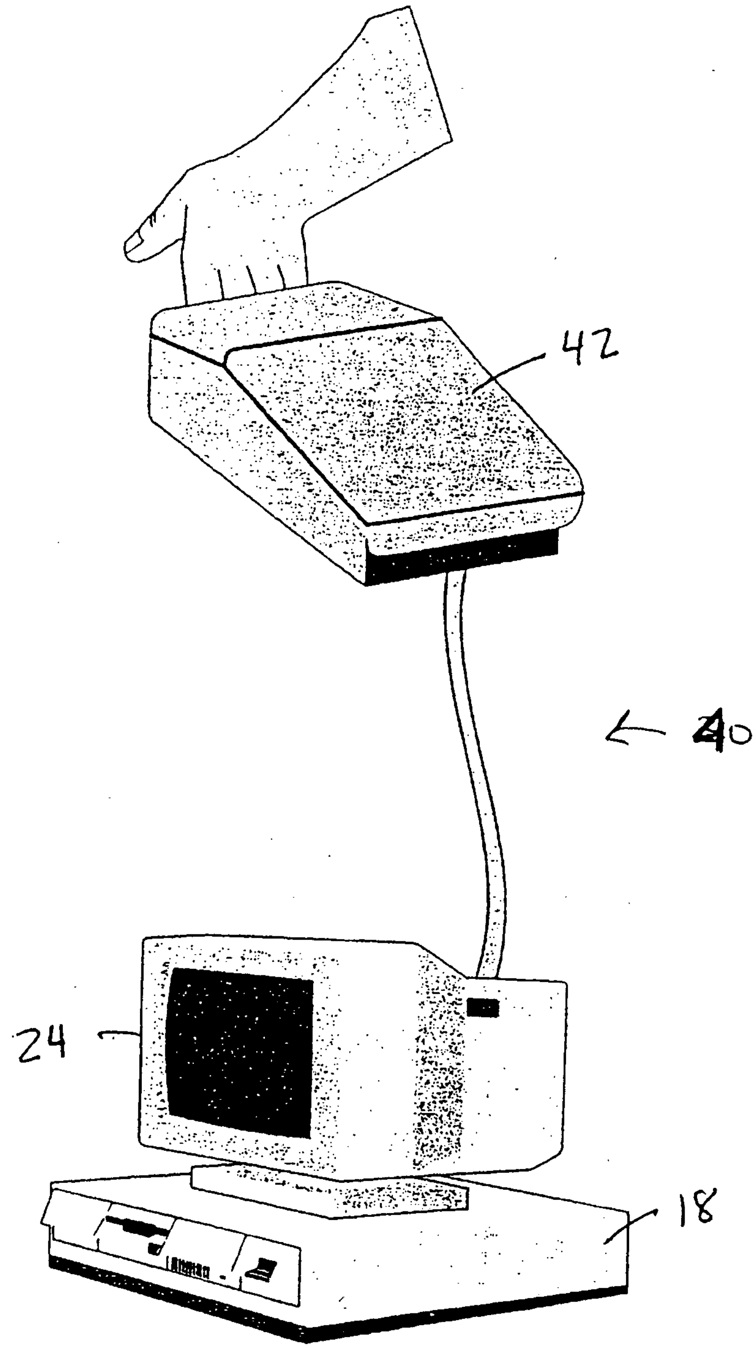


Figure 8

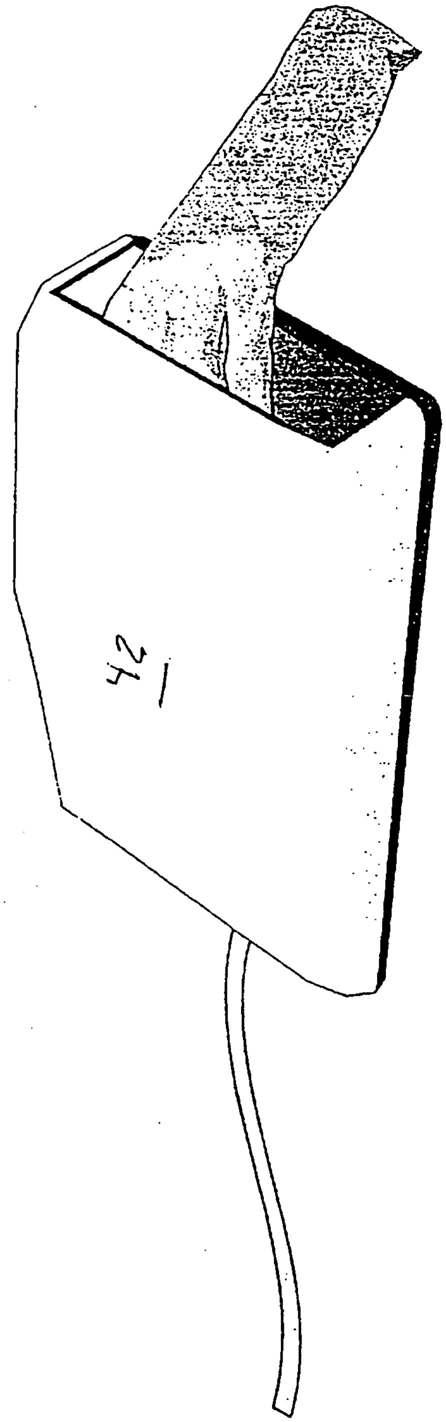


Figure 9

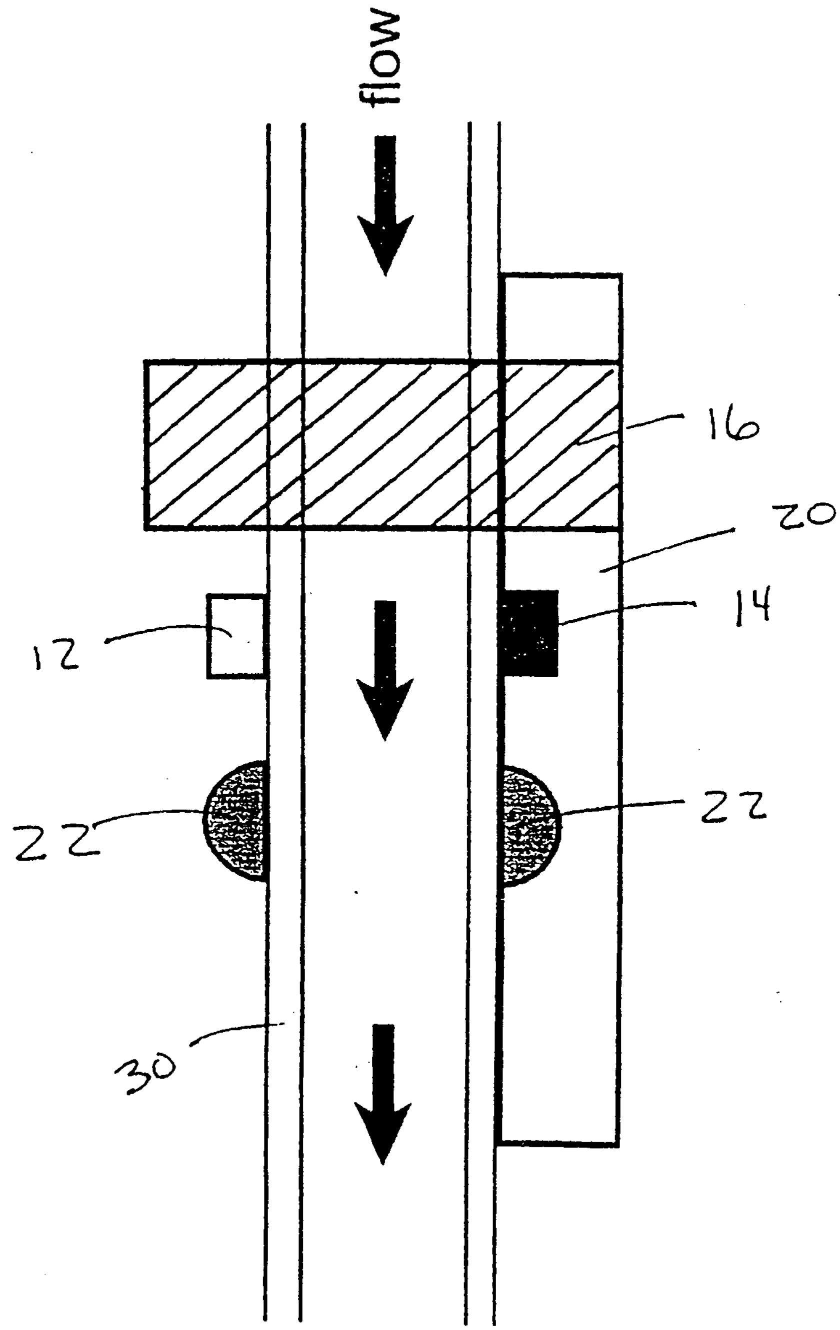


Figure 10

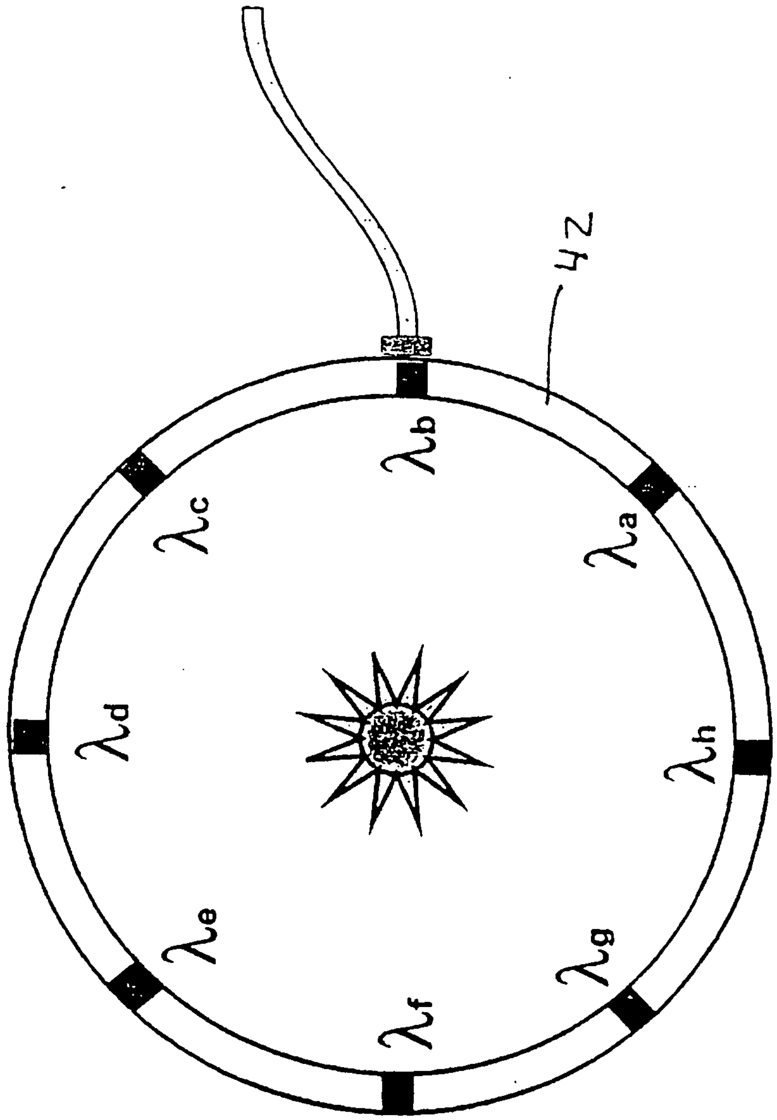
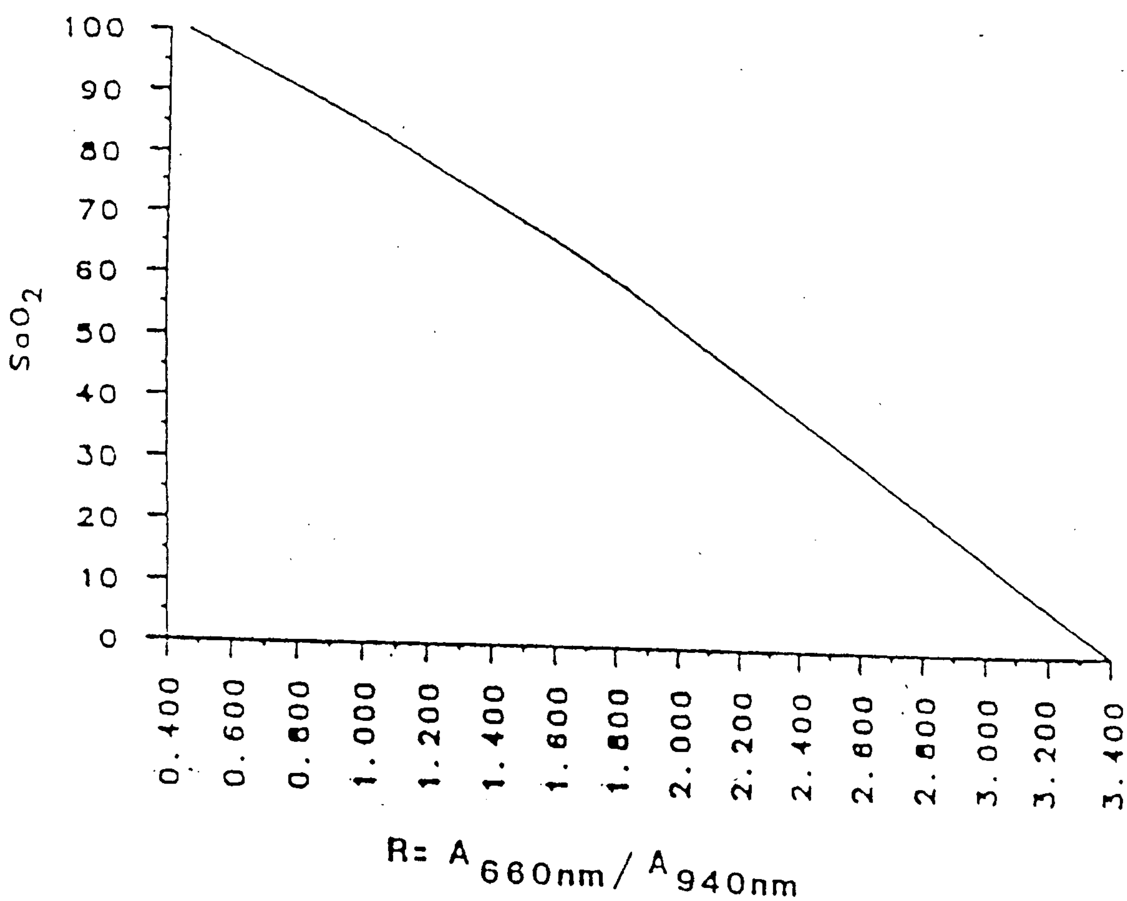

42
λ_b
λ_c
λ_a
λ_d
λ_h
λ_e
λ_g
λ_f

Figure 11

Calibration Curve



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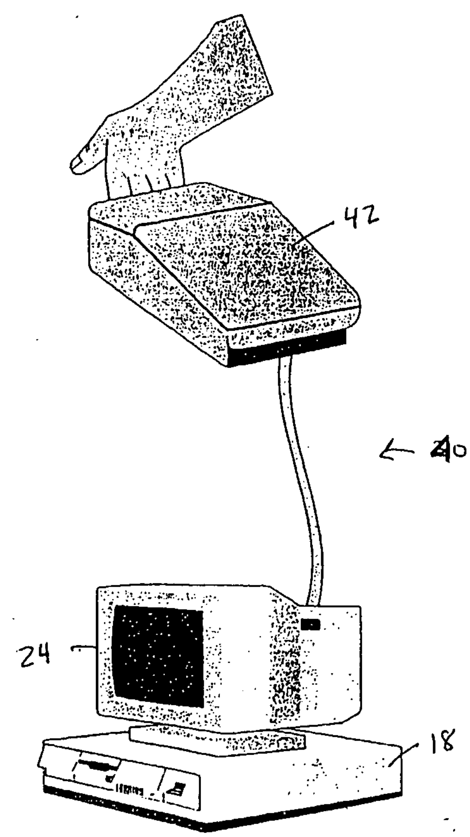
(57) Abstract

A device (10, 40) and method for noninvasively quantifying important physiological parameters in blood. The device and method utilize changes in molecular behavior induced by thermal energy of change to facilitate the measurement of the physiological parameters in blood. Oxygen saturation, partial pressure of oxygen, partial pressure of carbon dioxide, concentration of bicarbonate ion and total carbon dioxide, acid-base balance, base excess, hemoglobin level, hematocrit, oxyhemoglobin level, deoxyhemoglobin level, and oxygen content can all be determined quickly, easily, and continuously. There is no need for skin puncture or laboratory analysis.



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U.S. : 356/39, 41; 600/322, 323, 326, 334

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X --- Y	US 5,131,391 A (SAKAI ET AL) 21 JULY 1992, ENTIRE DOCUMENT.	14-18, 20-27, 30, 32, 33, 38-42 --- 19, 28, 29, 31, 34-37
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